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EFFECT OF EXCESS SUGARS ON THE PERFUSED RABBIT HEART*

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ACTIVE controversy concerning the fuel of the heart has continued for several decades. Although dextrose was long considered the only or chief utilizable foodstuff,[4, 17] it was early appreciated[19] that the quantity actually consumed by the heart was only a few milligrams per gram of heart muscle per hour. Later, more critical investigations employing improved and refined methods of study eliminated or evaluated the appreciable glucose disappearance that results from bacterial decomposition,[3] from glycolysis in the blood,[8] and from oxidation in the lungs,[8, 22] and it is now believed that the heart uses probably only 0.2 or 0.3 mg., and possibly less than 0.1 mg., of glucose per gram of muscle per hour.[4, 7, 22]

In recent years lactic acid has gained increasing recognition in the energy metabolism of the heart,[6, 13, 22, 23] but dextrose is still regarded as a probably important accessory fuel, or perhaps even as the major precursor of the lactic acid.[8] Finally, dextrose appears favorably to influence the synthesis of phosphocreatine.[20, 26] It is thus evident that dextrose plays a significant if not a major role in this still insufficiently elucidated phase of cardiac metabolism.

In spite of the diversity of opinion from the physiologic laboratories concerning the actual fuel or fuels of the heart, their relative importance, and the precise role played by dextrose, there has been a growing clinical interest, evident particularly in the foreign literature, in the liberal parenteral administration of dextrose in acute and chronic heart failure.[14, 27, 29]

Since judgment of the efficacy of this sugar has been based almost entirely on clinical impression, and opinion has been conflicting,[22, 23] it

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was considered desirable to attempt a more objective study on animals in the laboratory. Abundant consideration has long been given to the metabolic aspects of heart muscle physiology.[4] Merely to demonstrate, however, that heart muscle may under certain conditions of fuel supply increase its oxidative metabolism does not necessarily indicate that the organ has become more efficient directly as a result of its greater consumption of a more generously provided foodstuff. The diseased, dilated, anoxic, or otherwise failing heart is perhaps a less efficient mechanism and may convert too little of its oxidative energy into useful work. Metabolic studies alone, therefore, are not adequate quantitative criteria of efficiency; observations of the organ's actual performance are essential.

As the first step in determining the influence of sugars on cardiac behavior we sought the simplest surviving heart preparation and chose primarily to observe the effect of excess concentrations of dextrose on two characteristic phenomena, namely, myocardial activity and coronary flow. These observations appeared most conveniently obtainable in the isolated and saline-perfused heart, which is free from external nervous, hormonal, or metabolic influence.

METHODS AND PROCEDURE

The apparatus we have devised (Fig. 1) was based on the Langendorff method of perfusion.[16] Several modifications were introduced to permit ready shifting from one perfusate to any of three others without significant change either in perfusion pressure or temperature. Provision was also made for perfusing with either oxygen-saturated or with oxygen-deficient solutions.

The source of perfusion pressure was a Marriott bottle, *A*, filled with tap water, and suspended from the ceiling. The perfusion pressure, as determined by the height of the Marriott stopper above the level of the coronary ostia, could be varied as desired; it was usually fixed around 70 cm. Water from *A* displaced either oxygen or nitrogen from the gas pressure reservoirs *B* and *C*, forcing the gases into the preheated perfusates in incubator *D*. These gases served both as the final source of pressure and as supplementary means of saturating the perfusates. The oxygen-deficient solutions were prepared by bubbling nitrogen long and freely through bottles of perfusate. The solutions were then forced through a system of individual glass coils suspended in an agitated water bath in electric oven *E*. The outflow from the four coils converged into a single short insulated tube leading to the aortic cannula.

The heart *H*, suspended by a U-shaped cannula in the aorta, was enclosed in the covered chamber *F*, the interior of which was kept warm and moist by water circulating outside of the funnel receiving the coronary outflow. The outflow from the heart represented the flow through the coronary system only, since the pulmonary veins were ligated. This was attained by ligating the pulmonary vessels en masse and opening the pulmonary artery; the venae cavae were left open. The coronary flow was collected in a Condon tip recorder *G*, adjusted to empty and record electrically each collection of approximately 3 c.c. The apex of the heart was steadied by a spring clip. A thread leading from the right ventricular wall to a muscle lever recorded the amplitude and rate of contractions. Inasmuch as no sudden changes in rate were encountered, an artificial pacemaker to control this factor

was not considered necessary. The temperature T of the perfusates was kept near 37.5° C. This temperature tended gradually to decline as the coronary outflow diminished in the course of a prolonged experiment, yet with any single shift from one solution to another a change of 0.2° C. was seldom introduced and only rarely exceeded.

Hearts obtained from rabbits, killed by a sudden blow on the occiput, were used throughout. The perfusion was always begun with normal Ringer-Locke solution

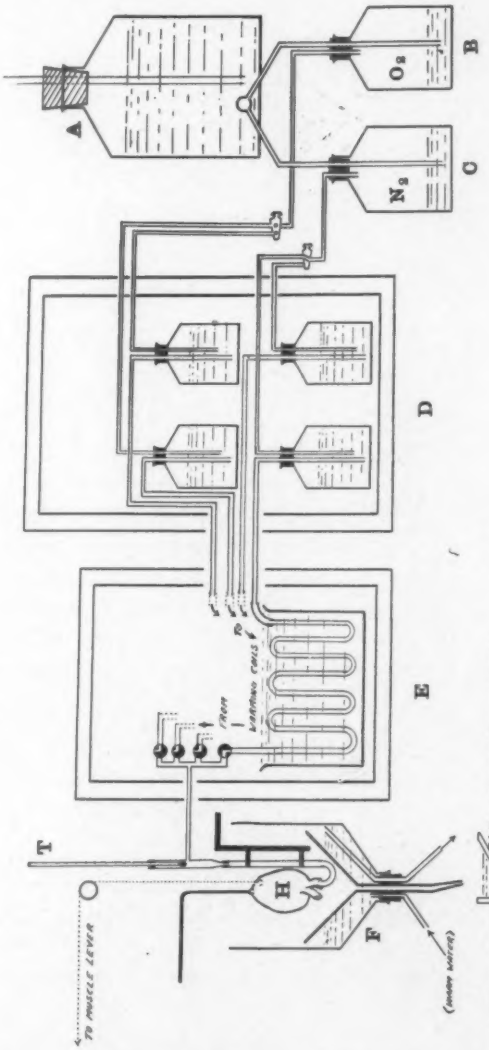

Fig. 1.—Diagram of apparatus for perfusion of isolated rabbit heart with four different solutions.

containing 0.1 per cent dextrose. Perfusion was continued for at least thirty minutes and until the action of the heart was uniform and satisfactory, after which the solutions under investigation were introduced. Ringer-Locke solution of nitrogen-ion concentration 8.0 to 8.4 was the basis for all the perfusates employed; the composition of the perfusate was sodium chloride 0.92 per cent, potassium chloride 0.042 per cent, calcium chloride 0.012 per cent, and sodium bicarbonate 0.03 per cent.

RESULTS

The results to be presented were in general consistent, regardless of whether the preparations were fresh and active or failing from prolonged perfusion. The final responsiveness of the seriously failing heart was usually proved at the end of an experiment by an injection of 0.3 mg. of epinephrine.

Hypertonic Dextrose Perfusates.—Nineteen hearts were perfused with Ringer-Locke solution to which excessive amounts of dextrose were added. The experiments were of two types. In one group of fifteen hearts a perfusate in which the dextrose content was raised to 1 per cent was selected as corresponding to the higher concentrations obtained clinically with intravenous dextrose therapy.[24, 32] In the other four experiments a perfusate made twice osmolar with 5.6 per cent dextrose was chosen primarily to observe the effect of hypertonicity. Control experiments employing equivalent concentrations of sucrose are described below.

With the 1 per cent dextrose perfusate a stimulating effect on the heart muscle was observed consistently in thirteen hearts, and no effect occurred in three hearts, including one in which an earlier positive effect was not reproducible. The coronary flow was increased in eleven of the fifteen hearts, and no response was obtained in seven hearts, including three which showed positive effects during another trial. Figs. 2, 3, 4, and 6 illustrate positive effects on the heart muscle obtained with the 1 per cent dextrose perfusate; and Figs. 2, 4, and 6 show increase in coronary flow preceding the increase in stroke amplitude.

When the 5.6 per cent dextrose perfusate was employed in four hearts, the myogram showed either no stimulation or actual depression in two hearts, stimulation in one heart, and inconsistent effects in another. The coronary flow was increased in four of the five hearts. Fig. 5 gives an example of both positive effects with the 5.6 per cent dextrose perfusate.

The observed "stimulating effect on the heart muscle" generally consisted of a gradual augmentation in the amplitude of the cardiac contractions, which usually began almost immediately on the introduction of the effective perfusate and persisted for several minutes; the amplitude then gradually declined again until it was approximately what it had been under the original control perfusate. Increases in coronary flow attributable to a change in perfusate always appeared promptly on the introduction of the perfusate; if effective, they lasted for from one to several minutes, after which the flow then usually declined moderately. The augmentation of the stroke amplitude was almost invariably preceded slightly but definitely by the increased coronary flow, and sometimes, as in Fig. 9, the coronary flow was increased even in hearts so feeble that no stimulation of the muscle was evident in the

myogram. These last observations are important, for they answer the criticism, at least for these cases, that the increased coronary flow might have been apparent only, not real, and due to the emptying of the right

Fig. 2.—Rabbit heart. Typical positive effect of hypertonic dextrose perfusate on myogram and coronary flow.

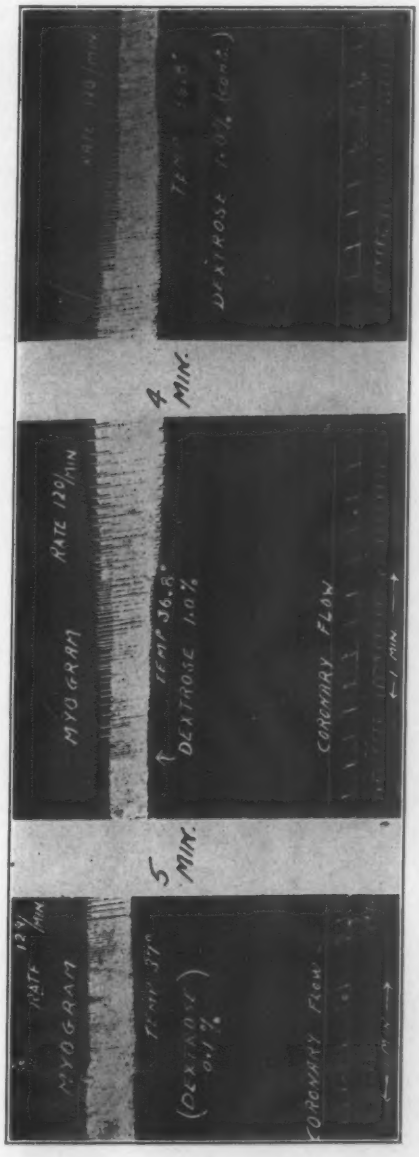

Fig. 3.—Rabbit heart. Positive effect of hypertonic dextrose perfusate on myogram. No effect on coronary flow.

ventricular cavity accompanying its increased vigor of contraction. Another error recognized as inherent in this method of recording coronary flow, but one which does not alter our interpretations, is the

leak past the aortic valves of perfusate which is added to that coming from the heart by way of the coronary vessels. Our interpretations concerning the coronary circulation, however, are based not on absolute values but on changes in flow; no significant changes in aortic leak would be expected with our uniformly maintained aortic pressures. Furthermore, changes in flow usually preceded any increased activity

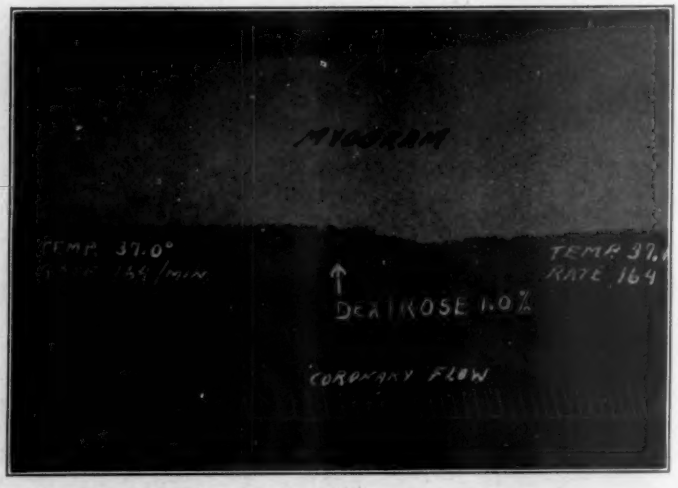

Fig. 4.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Change to 1 per cent dextrose results in increase in myogram and coronary flow.

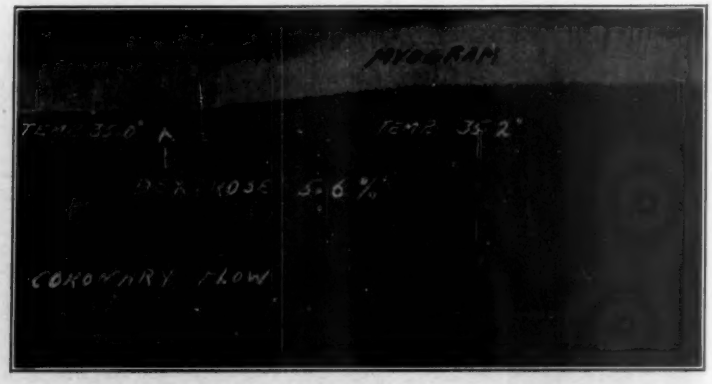

Fig. 5.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Changing to 5.6 per cent dextrose results in transient increase in myogram and coronary flow.

of the heart which might have disturbed the anatomic relationships of the aortic leaflets and altered the competency of the valves. Finally, augmentation of flow occasionally occurred without either simultaneous or subsequent stimulation of the muscle.

Hypertonic dextrose, therefore, appeared usually to increase the coronary flow, but muscular stimulation was more regularly evident only with the 1 per cent dextrose perfusate.

Each of two rabbits was given one intravenous injection of 50 mg. caffeine sodiobenzoate per kilo, followed in two minutes by 0.2 mg. epinephrine. This procedure is known to result constantly in myocarditis in rabbits.[9, 12, 15] Several weeks later these animals were sacrificed and the hearts perfused as above with isotonic and hypertonic

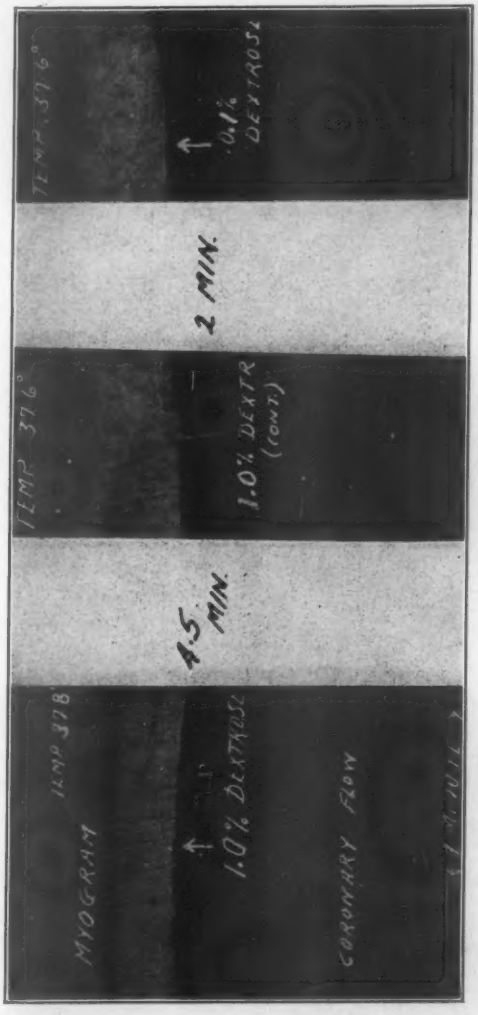

Fig. 6.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Changing to 1 per cent dextrose results in increased myogram and coronary flow.

dextrose solutions. Moderate increase of coronary flow and augmentation of the myogram indistinguishable from that already described with previously uninjured hearts were observed with the 1 per cent dextrose perfusate. The injured hearts showed pericardial adhesions and gross scarring of the myocardium.

That the heart may not accumulate a significant fuel reserve when generously supplied with an excess of dextrose is evident from Fig. 7.

This heart had been perfused for fifty minutes with a Ringer-Locke solution containing 1 per cent dextrose, yet on changing to a dextrose-free perfusate progressive failure promptly set in.

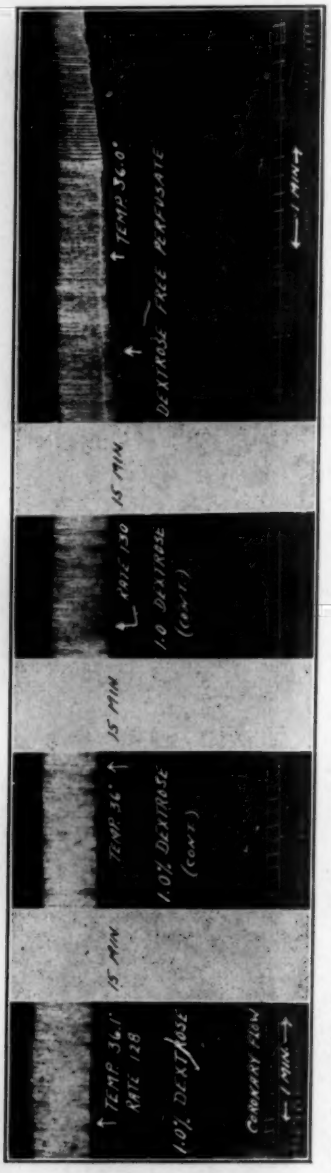

Fig. 7.—Rabbit heart. Perfusion with hypertonic dextrose for fifty minutes is followed by rapid failure of contraction when a dextrose-free perfusate is introduced.

Fig. 8.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Introduction of insulin-containing perfusate is followed by sustained augmentation of myogram, with slight further stimulation when 1.0 per cent dextrose replaces 0.1 per cent dextrose perfusate.

To observe the effect of excess dextrose in the presence of insulin, this hormone was injected into the perfusing cannula in several experiments, and in two other experiments 100 units of insulin were mixed with each liter of perfusate. The simple injection of insulin into the perfusing

cannula was apparently without effect with either the 0.1 per cent or the 1 per cent perfusates. The mixture of the insulin and the perfusate containing 0.1 per cent dextrose caused no increase in heart rate, but was followed by a moderate and fairly sustained increase in the stroke amplitude and the coronary flow in one experiment (Fig. 8); there were no significant effects in another experiment. In accord with these obser-

Fig. 9.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. No effect on myogram or coronary flow with either added insulin or excess dextrose.

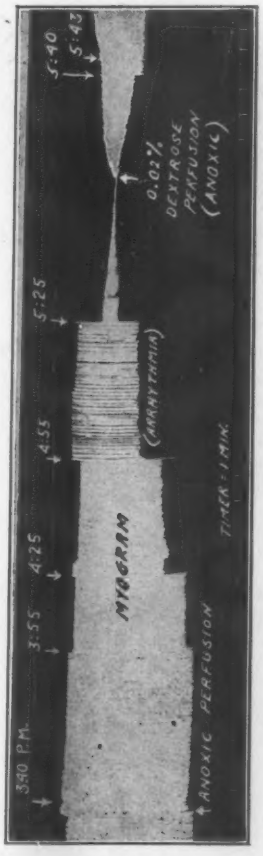

Fig. 10.—Frog heart. Shows gradual myocardial failure when perfused without oxygen and without carbohydrate. Prompt recovery of activity under continued anoxic conditions when dextrose is introduced.

vations are those of Bodo,[2] who observed a prolonged increase in cardiac tone in the heart-lung preparation when insulin was injected. When we introduced a 1 per cent dextrose solution along with the insulin perfusate in one experiment there followed a slight increase in the stroke amplitude but a diminution of coronary flow (Fig. 8); in a second experiment the admission either of insulin or of 1 per cent dextrose had no apparent effects (Fig. 9).

It appears from one of two experiments that insulin itself may on occasion slightly augment the coronary flow and stroke amplitude of the perfused rabbit heart. However, neither the myogram nor the coronary flow gives evidence of any greater benefits from excess dextrose when insulin is present in the perfusate.

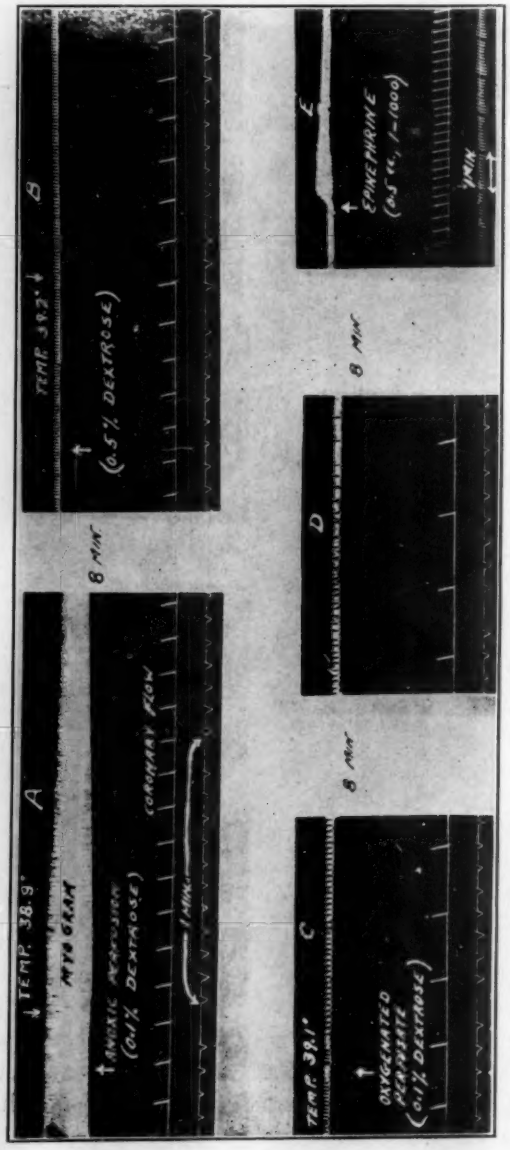

Fig. 11.—Rabbit heart. (Eight-minute intervals between segments.) *A*. Failure of myogram with anoxic perfusion. *B*. No beneficial effect from hypertonic dextrose perfusate. *C* and *D*. Tendency toward recovery on readmission of oxygenated perfusate. *E*. Myocardium still capable of being stimulated by epinephrine.

Oxygen-Deficient Hypertonic Dextrose Perfusates.—Freund and König[10] observed complete and sustained cessation of activity in the isolated frog heart when perfused in an atmosphere of nitrogen with

an alkaline Ringer solution free from oxygen and dextrose. The addition of dextrose alone to the perfusate produced dramatic resumption of rhythmic contractions. This effect we readily confirmed in each of two intact frog hearts kept in an atmosphere of nitrogen and

Fig. 12.—Rabbit heart. *A*. Decline of myogram under anoxic perfusion without improvement with hypertonic dextrose. *B*. Tendency toward recovery on readmission of oxygenated perfusate.

perfused through the postcaval veins after the method of Sollmann and Barlow.[28] The perfusate employed was Howell's frog heart Ringer solution brought to nitrogen-ion concentration 8.2 with 0.05 per cent sodium bicarbonate. Fig. 10 depicts the anoxic failure of the frog heart and its prompt revival with dextrose.

Pollack and Wilder,[26] working with dogs, argued that anoxemia caused a breakdown of the phosphocreatine mechanism as a source of energy, offering this in explanation of the damaging effect of anoxemia in heart disease. Their observation that the intravenous administration of glucose is followed by a fall in the serum phosphates and their deposition in skeletal and cardiac muscle led them to the conclusion that glucose, through its synthesizing action on phosphocreatine, can to a certain extent overweigh or overbalance the hydrolyzing effect of anoxemia on phosphocreatine.

The above indications that the metabolism of the heart muscle may be fundamentally altered in anoxemia led to the following experiments with oxygen-deficient perfusates:

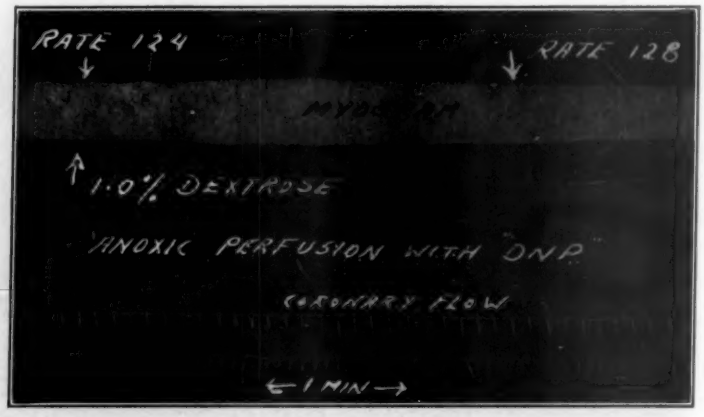

Fig. 13.—Rabbit heart. Perfusion begun with oxygen-free 0.1 per cent dextrose solution. Slight augmentation of myogram on changing to 1 per cent dextrose.

After normal and uniform activity had become established in the excised and perfused rabbit heart, an oxygen-deficient Ringer-Locke solution was introduced. Slow and gradual failure followed in each of the seven hearts so treated; a typical example of this effect is illustrated by Fig. 11. To accelerate this failure, for purposes of convenience, alpha-dinitrophenol (1:20 million dilution) was added to the perfusate in five additional experiments. This concentration had been found to stimulate the activity of the heart without apparent injury.[11] The administration of 1 per cent dextrose was followed by a transient stimulation of muscular contraction, or a temporary retardation of previous gradual failure in six out of ten such failing hearts. The coronary flow in these experiments was increased, decreased, and unaltered in about equal numbers. Fig. 12 depicts simple anoxic failure without evident benefit from excess dextrose, and Fig. 13 illustrates a slight improvement with 1 per cent dextrose in anoxic failure accelerated by alpha-dinitrophenol.

If the asphyxial depression of the rabbit heart was permitted to proceed to complete cessation of activity, no revival could be accomplished by the administration of dextrose, as in the case of the frog heart.

Apparently the introduction of hypertonic dextrose perfusates under anoxic conditions caused only such changes in mechanical activity of the heart and alterations in coronary flow as had already been observed under conditions of adequate oxygenation. It must be remembered, in applying our results to the conclusions of Pollack and Wilder,[26] that our perfusates were the Ringer-Locke solution, and were lacking in utilizable phosphates.

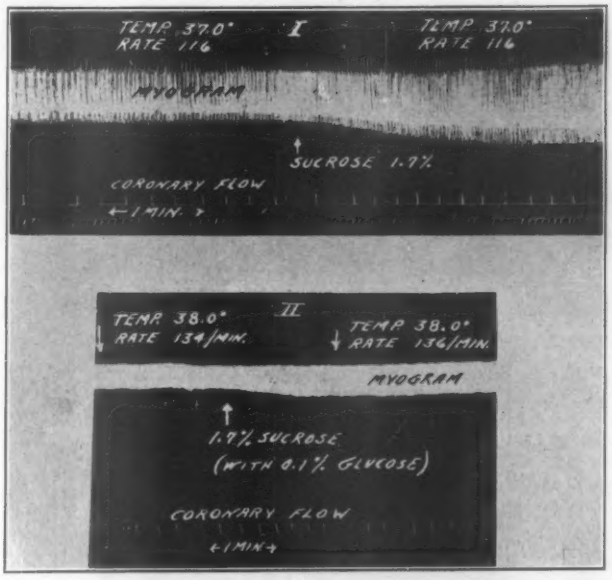

Fig. 14.—Rabbit hearts. Perfusion begun with 0.1 per cent dextrose solution. Both experiments show augmentation of myogram and coronary flow on addition of 1.7 per cent sucrose.

Sucrose Perfusates.—To determine whether the results obtained with dextrose were metabolic or osmotic in character, control observations were made with the nonutilizable sugar, sucrose. Sucrose was added to the Ringer-Locke solution, which contained the usual 0.1 per cent dextrose, in two concentrations corresponding to the two concentrations of excess dextrose employed in previous experiments, namely, 1.7 per cent and 10.4 per cent sucrose, osmotically equivalent to 0.9 per cent and 5.5 per cent dextrose respectively.

In the course of any single experiment the corresponding sucrose and dextrose perfusates were always compared. In seven hearts studied in this manner the results on muscular contraction were about equally divided between augmentation and no effect, both for the higher and the lower concentrations of sucrose. The coronary flow, however, was

definitely increased by the higher concentration of sucrose in each of three hearts, and with the lower concentration an increased flow resulted in three out of four hearts. Fig. 14 shows two experiments in which the introduction of a hypertonic sucrose perfusate resulted in augmentation of the stroke amplitude and slight increase in coronary flow. Fig. 15 illustrates the essential similarity of effects from either dextrose or

Fig. 15.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose with transient stimulation of myogram and coronary flow under 5.6 per cent dextrose and later a similar response to an equivalent concentration of sucrose.

sucrose in excess concentrations. In general, then, the results with sucrose are seen to be similar to those obtained with dextrose concentrations of equal tonicity.

It is re-emphasized that in all the preceding experiments with sucrose the perfusates always contained 0.1 per cent dextrose also. One heart, however, was perfused with dextrose-free Ringer-Locke solution containing 0.1 per cent sucrose, and the anticipated prompt failure was noted.

DISCUSSION

Although some variation of results was obtained in these experiments, such inconsistencies are not unexpected under the relatively unphysiologic conditions surrounding the perfused isolated heart. On the basis of a reasonably large number of experiments, however, it seems permissible to venture certain conclusions concerning the myocardial and coronary effects of sugars furnished in excess concentrations.

The old observation that dextrose is an acceptable ingredient of a perfusate for the heart was again simply confirmed by these experiments. A small quantity of this sugar in a perfusate suffices to sustain contraction of the heart. Sucrose, however, failed as a fuel substitute for dextrose, as Maclean and Smedley observed in 1913.[21]

But acknowledgment that dextrose has definite value as a cardiac fuel need not imply that its excessively liberal administration will increase utilization, storage, or work. In fact, previous investigators have already suggested a negative answer to this question. Cruickshank and Startup[5] found only a 10.5 per cent increase in sugar oxidation in the heart-lung preparation in the presence of hyperglycemia, and the increased oxidation was not in proportion to the degree of hyperglycemia. Furthermore, since it is now apparently established[4, 6] that the heart utilizes only a fraction of a milligram of dextrose per gram of muscle per hour, it seems entirely reasonable that the sugar content of the blood and the abundant stores in the muscles, skin, and other tissues are in themselves ample to meet even a great increase in the oxidative capacity of the heart. Finally, Starling and Visscher[30] found that although the failing heart may utilize as much oxygen and liberate fully as much energy at any fiber length as the normal heart, the failing organ converts much less of this energy into work; in other words, the efficiency of the failing heart is definitely lower. It seems a logical conclusion, therefore, that the essential need of the failing heart does not lie in its demand for greater quantities of fuel.

Whether or not insulin appreciably increases the glucose utilization of the heart is still disputed.[4] Visscher and Müller[31] found no evidence that insulin had any direct stimulatory effect on the oxidative metabolism of the isolated heart. Insulin apparently did not increase the rate of disappearance of sugar from the heart-lung preparation in Plattner's experiments,[25] and Cruickshank and Startup,[5] in similar preparations, found that the addition of insulin resulted in only a 3.6 per cent increase in sugar oxidation even in the presence of hyperglycemia. Our experiments support the view that the addition of insulin to the excess of dextrose does not augment in any significant manner the effects obtained with dextrose alone.

Inasmuch as our results were essentially the same with either dextrose or nonutilizable sucrose, it is probable that the myocardial and coronary

effects we observed were not metabolic but osmotic in character and were derived primarily from alterations in muscle tone. Similar osmotic effects of hypertonic solutions on muscle tone have been described by Barbour and Rapoport[1] in studies on the intact uterus of dogs.

SUMMARY AND CONCLUSIONS

An apparatus is described which will permit long perfusion of an isolated mammalian heart with several readily interchangeable perfusates at constant temperature and pressure.

Ringer-Locke perfusates containing excess concentrations of dextrose usually cause moderate and transient increase of the coronary flow, leading immediately to augmentation of the stroke amplitude.

The apparently similar myocardial and coronary stimulation observed with perfusates containing excess concentrations of nonutilizable sucrose suggests that all the sugar effects are osmotic rather than metabolic.

Perfusion with Ringer-Locke solution containing sucrose in place of dextrose results in early failure of the heart.

There is no evidence that long perfusion with an excess of dextrose results in the storing or building up of other reserve fuel.

The myocardial and coronary effects are essentially the same whether or not insulin is supplied with the excess of dextrose, whether or not the perfusates are adequately oxygenated, and whether or not the hearts have been previously damaged by drugs.

Although the activity of the frog heart which has been subjected to anoxic failure is promptly restored by the administration of dextrose, no such revival of a similarly depressed rabbit heart can be accomplished with dextrose alone.

There is no evidence from our experiments that dextrose furnished in greater than the usual physiologic concentration of 0.1 per cent offers more than a fleeting functional advantage to the isolated rabbit heart when perfused with Ringer-Locke solution.

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HEMODYNAMIC STUDIES IN EXPERIMENTAL CORONARY OCCLUSION*†

V. Changes in Arterial Blood Pressure

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THE published reports on the effect of experimental coronary artery occlusion on arterial blood pressure have concerned themselves almost entirely with the immediate changes which follow this procedure. There has been no unanimity expressed as to the sequence of events. Thus, in 1867, von Bezold[1] reported a fall in arterial blood pressure occurring simultaneously with the appearance of cardiac irregularities following coronary occlusion in rabbits. Cohnheim and Schulthess-Rechberg[2] made similar observations in dogs. Porter,[3, 4] who carried out extensive experimental researches in this field, observed that there was a short and rapid rise in arterial blood pressure immediately after the vascular occlusion in dogs and that in some experiments this was followed by a fall. Michaelis[5] reported a slow or rapid fall in arterial blood pressure after coronary ligation in rabbits. Wassiliewski[6] injected lycopodium spores into the coronary vessels of rabbits and dogs. Soon after the injection there was a rapid fall in blood pressure. In rabbits this was preceded by a rise.

Of the more recent experiments, Sutton and Lueth[7] observed a rapid fall in blood pressure amounting to 30 to 50 mm. Hg following partial compression of the dog's coronary artery. In vagotomized animals the vascular occlusion was followed by no alteration in the blood pressure. Feil, Katz, Moore, and Scott[8] observed "surprisingly small changes" in the arterial blood pressure following coronary artery occlusion in dogs. There was an apparently constant drop of only 5 to 20 mm. Hg in 6 out of 19 animals. In 4 dogs a temporary drop was followed by a return to normal or higher levels, and in 5 a rise of 10 to 30 mm. Hg took place. In every instance with premature beats and paroxysmal tachycardia a drop of 20 to 40 mm. Hg was recorded. Cox and Robertson[9] studied the blood pressure of dogs over a period of months before and after coronary occlusion and observed no appreciable differences between the preligation and postligation blood pressure levels.

The clinical observations dealing with blood pressure changes following coronary occlusion have been followed more thoroughly. It is

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currently accepted that myocardial infarction is generally associated with a fall in arterial blood pressure. Fishberg, Hitzig, and King,[10] pointed out that this fall takes place only in those cases of myocardial infarction in which evidences of shock appear. They believe that in instances of myocardial infarction in which the clinical features are predominantly those of cardiac insufficiency with intense pulmonary engorgement, the blood pressure tends to be maintained at a level relatively close to that prevailing prior to the infarct, or it may even rise.

In a recently reported series of studies on experimental coronary occlusion in dogs, we have shown that the only hemodynamic changes which deviate appreciably from those observed in controls under similar experimental conditions were an immediate diminution in average cardiac output and delay in cyanide circulation time. These observations were based on a study of the changes produced by anesthesia alone, anesthesia followed by thoracotomy without coronary ligation, and by coronary ligation performed in the open chest,[11] in the closed chest (by the double carrick bend knot[12]), in denervated hearts,[13] and in stellate-ganglionectomized dogs.[14] Although an immediate fall in blood pressure was recorded following occlusion of the left anterior descending coronary branch under the various conditions mentioned above, with the exception of the denervated hearts this was no greater than that found in the control animals. From these observations it was concluded that this immediate fall in arterial blood pressure was due to the anesthesia or thoracotomy, and not to the vascular occlusion. In the sympatheticovagotomized dogs there was an immediate fall in blood pressure which exceeded that of the controls.

The present report concerns itself with further studies on the arterial blood pressure under the various experimental conditions mentioned above. The arterial blood pressure was measured by puncturing the femoral artery with a 19-gauge needle which was attached by a three-way stopcock to a syringe and mercury manometer. The readings were made during the immediate preligation period, during the immediate postligation period, twenty-four hours after the vascular ligation, and one week later. Eighty-two mongrel dogs weighing between 10 and 20 kilograms were employed in the experiments. The details of the experimental procedures are recorded in our earlier reports. Simultaneously with the blood pressure readings, other hemodynamic studies were carried out in a number of the dogs. All readings and tests were made under nembutal anesthesia.[11]

RESULTS

As will be seen in Table I, in which the preligation value is recorded as an average value for the group, or as 100 per cent, the anesthetic alone (Group A) produced no appreciable change other than a moder-

TABLE I

BLOOD PRESSURE CHANGES AFTER VARIOUS PROCEDURES

GROUP		*Average Mean Blood Pressure Changes in Mm. Hg*				*Average Per Cent Mean Blood Pressure Changes*			
		PRELIGATION*	POSTLIGATION†	24 HOURS LATER	ONE WEEK LATER	PRELIGATION	POSTLIGATION	24 HOURS LATER	ONE WEEK LATER
A	Anesthesia controls	123 (10)‡	125 (10)	112 (6)	138 (4)	100	102	91	112
B	Thoracotomy controls (No ligation)	148.3 (10)	133 (10)	117.7 (10)	132 (9)	100	90	80	89
C	Thoracotomy + left anterior descending coronary branch ligation	152 (12)	127 (12)	94 (11)	99 (6)	100	84	62	65
D	Left anterior descending coronary branch ligation (closed chest)	118 (10)	120 (10)	71 (5)	100 (3)	100	102	60	85
E	Denervated heart: Left anterior descending coronary branch ligation (closed chest)	131 (10)	115 (10)	--	--	100	88	--	--
F	Denervated heart: Left ventricular muscle ligation (closed chest)	128.5 (10)	125.1 (10)	--	--	100	97	--	--
G	Thoracotomy + left anterior descending coronary branch ligation (stellate ganglia removed)	129 (10)	93 (10)	77 (10)	98 (4)	100	72	60	76
H	Left ventricular muscle ligation (closed chest)	146 (10)	131 (10)	112 (10)	117 (7)	100	90	77	80

*Twenty minutes before ligation.

†Twenty minutes after ligation.

‡The figures in parentheses indicate the number of animals in each group.

ate drop (9 per cent) twenty-four hours after its administration. Within a week (possibly soon after twenty-four hours), the blood pressure returned to preligation levels. It will be observed, however, that following thoracotomy under anesthesia (Group B), the average arterial blood pressure dropped 20 per cent within twenty-four hours. The blood pressure returned to within 10 per cent of the preligation level within one week. These blood pressure changes must be considered as the control base line for the experiments to be described.

Ligation of the left anterior descending coronary branch, whether performed in the open chest (Group C) or by the closed chest method (Group D[12]), produced no appreciable immediate fall in blood pressure. However, twenty-four hours after the vascular occlusion the blood pressure was decidedly lower than in the controls. At the end of the week the arterial blood pressure still remained low in the open-chest experiments but had risen toward normal values in the closed-chest experiments.

The immediate postligation arterial blood pressure level was lower in the dogs with denervated hearts (Group E) than in the corresponding controls (Group F). It has already been suggested[13] that this may be due to the absence of the masking effect of the usually wide fluctuations in vasomotor tone in animals with nerves intact, and possibly also to the interruption of some of the nervous pathways for compensatory vasoconstriction. Twenty-four-hour and one-week readings were not made in these groups because of the high mortality. In the stellate-ganglionectomized dogs (Group G) coronary ligation was followed by an immediate sharp drop in blood pressure which reached 60 per cent of its preligation value at the end of twenty-four hours and showed a relatively slow return to normal by the end of one week. Other effects of stellate ganglionectomy on the sequelae of coronary occlusion have been recorded elsewhere.[14]

Of considerable interest were the changes in blood pressure following ligation of small portions of left ventricular muscle in the closed chest experiments (Group H). Study of the cardiac output in this group of animals revealed no appreciable change from the anesthesia controls. Nevertheless, the arterial blood pressure sank 23 per cent at the end of twenty-four hours as compared with 9 per cent in the control groups.

DISCUSSION

The observations herein recorded indicate that coronary artery ligation in the dog's heart produces a definite fall in blood pressure. This, however, becomes conspicuous only twenty-four hours after the vascular occlusion and generally persists for at least one week. Since most of the reported experiments were not concerned with successive studies on the blood pressure following coronary occlusion, this fact seems to have been overlooked. In spite of the immediate fall in

cardiac output, an immediate fall in blood pressure does not occur probably because of compensatory vasoconstriction.

In our previous reports we have shown that the cardiac output tends to rise after twenty-four hours and that, moreover, the blood volume is not materially affected by the coronary occlusion. In spite of this, however, the compensatory vasoconstriction decreases twenty-four hours after the vascular ligation. The temporary immediate vasoconstriction is probably attributable to the decrease in cardiac output which stimulates the vascular vasosensitive areas. After twenty-four hours these mechanisms become readjusted to the lower output. The exact nature of these adjustments remains obscure.

SUMMARY

1. Twenty-four hours after experimental occlusion of the left anterior descending coronary branch in dogs there occurs a decided fall in blood pressure which generally persists for at least one week.

2. Twenty-four hours after ligation of left ventricular myocardium by the closed chest method a fall in blood pressure also occurs. This fall is smaller than that following the vascular occlusion.

3. A comparison is made with control observations, and the mechanism for the decrease in blood pressure under these conditions is discussed.

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BUNDLE BRANCH AND INTRAVENTRICULAR BLOCK IN ACUTE CORONARY ARTERY OCCLUSION*†

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IN THIS report we have analyzed the disturbances in intraventricular conduction observed in 375 cases of acute coronary artery occlusion with reference to their incidence, clinical and electrocardiographic features, prognosis and pathogenesis. All records in which the QRS interval was prolonged to 0.12 sec. or more were considered. These included all types of bundle branch and intraventricular block. We have been impressed by the frequency of such intraventricular conduction disturbances in this disease and their association with a specific lesion in the heart, namely, infarction of the interventricular septum. The common occurrence of the latter has already been pointed out.[1]

Previous investigators[2-5] have demonstrated that bundle branch block is caused by involvement of the conduction system situated in the interventricular septum, usually as a result of disease of the coronary arteries. The association of bundle branch and intraventricular block with acute coronary occlusion has often been reported,[6-26] and a few authors[27-30] have drawn attention to its frequency. The fact that the sudden appearance of bundle branch block may be the first electrocardiographic sign of acute coronary occlusion has not been sufficiently stressed.

INCIDENCE

A review of the conduction disturbances in several large series of acute coronary artery occlusion reported in the literature[28, 30-38] revealed that bundle branch block was present in 6.7 per cent of 930 cases and intraventricular block in 7.3 per cent of 831 cases, a combined incidence of 12 per cent in 1058 cases. The highest figures, up to 28 per cent, were observed in the series of autopsy cases,[28, 36-38] indicating the increased mortality rate associated with intraventricular block. In our series of 375 patients defective intraventricular conduction, as evidenced by widening of the QRS interval to 0.12 sec. or more, was present in 57, or 15 per cent (Table I). Marked prolongation of the QRS interval to 0.18-0.20 sec. occurred in 4 patients, mod-

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TABLE I

BUNDLE-BRANCH AND INTRAVENTRICULAR BLOCK IN CORONARY OCCLUSION; CLINICAL AND POSTMORTEM DATA IN 57 PATIENTS

CASE	SEX	AGE	CLINICAL ATTACK	HYPERTENSION	CARDIAC ENLARGEMENT	HEART FAILURE	QRS DURATION	BLOCK	ONSET	DURATION	P-R	ECG	MORTALITY	POSTMORTEM	
														OCCLUSION	INFARCTION
1. P.B.	M	47	1	?	++	++++	0.20	LBB	1 day	Permanent	0.30	?	0		
2. R.N.	F	66	2	+	+++	+++	0.18	LBB	1st record	Permanent	0.24	?	0		
3. M.E.	M	72	2	+	++	+++	0.18	RBB	20th day	Until death	0.18	T-1	+	LAD.	Ant. wall. L. V.; ant. sep.; sep. perfora.
4a. D.F.	M	58	2	+	+++	++++	0.16	LBB	1 day	Permanent	0.24	T-1	0		
4b. D.F.	M	59	3	+	+++	++++	0.18	RBB	1 day	Permanent	0.26	T-3	0		
5. D.B.	M	56	2	+	+	++	0.16	LBB	1 day	Until death	0.16	T-1	+	Acute and old LAD.	Anterior L. V.; lower half septum
6. M.C.	M	50	2	+	+++	++	0.16	I-V	1st record	2 weeks	0.20	?	0		
7. S.D.	F	47	1	+	+	0	0.16	LBB	1st record	Few weeks	0.22	?	0		
8. A.G.	M	48	2	+	+	+++	0.16	I-V	1st record	Until death	0.16	?	+	Old LAD and left circ.; acute right.	Post. L. V.; post. septum.
9. P.S.	F	55	2	+	+	++	0.16	I-V	1st record	Until death	0.14	T-1	+	Old LAD. and right; acute LAD.	Ant. & post. L. V.; entire septum.
10. R.W.	M	69	1	+	+	++	0.16	RBB	1 day	Until death	0.16	T-1	+		
11. L.B.	M	67	2	?	++	+++	0.15	LBB	Before attack	Permanent	A.F.	?	0		
12. J.B.	M	59	2	?	+++	+++	0.15	LBB	1st record	Until death	0.16	?	+	Old left circ. & acute right.	Apex L. V. & ant. sept.; aneurysm apex.
13. A.L.	F	57	2	+	++	+	0.15	LBB	1 day	Permanent	0.22	?	0		
14. S.F.	M	47	2	+	+	+++	0.15	RBB	1 day	Until death	0.16	T-1	+	Old rt. & acute LAD, left circ. & right.	Ant. & post. L. & Rt. V.; entire septum.
15a. S.G.	M	68	1	+	++	+	0.12	LBB	1st record	Permanent	0.16	T-1	0		
15b. S.G.	M	69	2	+	+++	+++	0.15	LBB	Gradual	Until death	0.16	?	+	Old LAD and right; acute right.	Old ant. L. V. and lower septum.

TABLE I—CONT'D

								Atypical							
16.	M.T.	M	66	2	+	++	+++	0.15	RBB	10 day	Until death	0.20	T-1	+	
17.	I.L.	F	78	2	+	++	+++	0.15	RBB	1st record	Until death	H.B.	T-3	+	Old LAD, left & right circ.; acute R. and LAD.	Post. L. & Rt. V.; post. septum.
18.	B.F.	M	41	2	+	++	+++	0.15	LBB	1st record	Permanent	0.18	T-1	0		
19.	E.L.	M	47	1	+	0	0	0.15	RBB	Before admission	Permanent	0.16	?	0		
20.	D.R.	M	62	2	?	++	+++	0.15	RBB	1st record	Until death	0.22	T-3?	+	Old & acute LAD; ant. & post. L.	Ant. & Post. L. V.; ant. ⅔ septum.
21.	J.S.	M	50	1	?	0	++++	0.15	I-V	1st record	Until death	0.15	T-1	+		
22a.	N.R.	M	57	2	+	+++	+++	0.12	LBB	1 day	Permanent	0.22	T1-2-3	0		
22b.	N.R.	M	57	3	+	+++	+++	0.15	LBB	39 day	Permanent	0.24	T1-2-3	0		
23.	D.F.	M	75	2	+	++	++++	0.14	LBB	1st record	Until death	0.40	T-1?	–	Acute & old right.	Post. L. V. with aneurysm
24.	M.G.	M	56	1	+	+++	+++	0.14	LBB	1st record	Permanent	0.20	?	0		
25.	M.G.	M	60	2	+	+	++	0.14	LBB	1st record	Until death	0.18	T-1	+		
26.	G.M.	M	35	1	+	0	+	0.14	LBB RBB	1 day 2 day	1 day Permanent	0.16	T-1	0		
27.	S.L.	M	67	3	?	+++	+++	0.14	RBB	1st record	Until death	0.16	T-3	+	Old LAD & right; acute right.	Post. L. V.; post. septum
28.	M.R.	M	60	1	+	++	+++	0.14	LBB	1st record	Permanent	0.10	?	0		
29.	E.D.	M	63	3	+	+++	++++	0.14	LBB	1st record	Permanent	0.16	?	+	Old LAD, L. & rt. circ.; acute LAD & RPD.	Post. L. V.; old ant. L. V.
30.	S.F.	M	86	1	0	0	0	0.14	RBB	1st record	?	0.14	T-3	0		
31.	E.M.	M	33	3	+	+++	+++	0.14	RBB	1st record	Permanent	0.24	?	+	LAD, L. & Rt. circ.	Ant. & post. L. V. and septum
32.	M.S.	M	73	1	+	++	+++	0.14	RBB	1st record	Permanent	0.14	?	0		
33.	I.G.	F	57	1	+	+	++	0.14	RBB	1 day	One day	0.20	T-3	0		
34.	M.K.	M	61	1	?	++	++	0.14	LBB	1st record	Permanent	0.20	T-1	0	LAD.	Ant. wall L. V.; ant. septum.

TABLE I—CONT'D

CASE	SEX	AGE	CLINICAL ATTACK	HYPERTENSION	CARDIAC ENLARGEMENT	HEART FAILURE	QRS DURATION	BLOCK	ONSET	DURATION	P-R	ECG	MORTALITY	POSTMORTEM	
														OCCLUSION	INFARCTION
35. O.L.	M	63	2	+	++	+++	0.14	I-V	1st record	Until death	0.16	T1-2-3	+	LAD; left and rt. circ.	Ant. & Post. L. V. and septum.
36. M.L.	M	66	3	+	++	++++	0.13	I-V	3 day	Until death	0.16	T-1	+		
37. W.B.	M	55	1	+	+	0	0.13	RBB	1st record	Permanent	0.14	?	0		
38. A.W.	M	50	1	0	0	0	0.13	RBB	1st record	Permanent	0.16	T-1	0		
39. J.S.	M	55	1	+	+	+	0.13	LBB	1st record	Permanent	0.14	T-1	0		
40. L.D.	M	61	1	+	+++	+++	0.13	RBB	1 day	Permanent	0.14	T1-2-3	0	LAD and right	Ant. & post. L. V.; entire septum.
41. C.A.	M	35	1	0	0	0	0.12	LBB	1 day	2 days	0.14	T-1	0		
42. L.B.	M	65	2	+	+	+	0.12	LBB	1st record	Permanent	0.18	T-3	0		
43. A.B.	M	65	2	+	++	++	0.12	LBB	1st record	Permanent	0.20	T1-2-3	0		
44. C.B.	F	72	2	+	++	++	0.12	LBB	1st record	Until death	H.B.	T-3	+	Old left circ.; acute right	Post. L. & Rt. V.; Post. septum.
45. D.C.	M	38	2	+	+	+++	0.12	LBB	1 day	Until death	0.22	T1-2-3	+		
46. J.K.	M	55	3	+	+	++	0.12	I-V	3 week	Until death	0.22	T1-2-3	+	Old LAD & rt.; acute LAD; L. & Rt. circ.	Ant. & Post. L. V.; entire septum.
47. A.L.	M	54	1	?	+	+	0.12	RBB	1st record	?	0.16	T-3	0		
48. C.L.	M	49	1	+	+	+	0.12	LBB	1st record	Permanent	0.24	T-1	0		
49. F.M.	M	62	2	0	+	++	0.12	I-V	1st record	Permanent	0.14	T-3	0		
50. J.M.	M	73	3	+	++	++	0.12	LBB	1st record	Permanent	0.18	T1-2-3	0		
51. E.R.	M	59	2	+	++	+++	0.12	LBB	1st record	Permanent	0.16	T-1	0		
52. J.U.	F	57	4	+	+++	++	0.12	LBB	1st record	Permanent	0.18	?	0		
53. A.Z.	F	53	2	+	+	++	0.12	LBB	Before attack	Until death	H.B.	T-3	+	Old LAD; L. & Rt. circ.; acute rt.	Post. L. & Rt. V.; post. septum.
54. G.B.	M	59	2	+	+	++++	0.12	I-V	1 day	Until death	0.14	T1-2-3	+	Old L. & Rt. circ.; acute LAD.	Ant. L. V.; ant. septum.
55. T.C.	M	31	1	0	0	0	0.12	I-V	1st record	Permanent	0.12	T-1	0		
56. H.R.	M	50	2	+	+	+	0.12	LBB	1 day	Permanent	0.16	T1-2-3	0		
57. S.M.	M	65	2	+	0	+	0.12	LBB	1 day	1 day	0.18	T-1	0		

erate prolongation to 0.14-0.16 sec. in 31 patients, and slight prolongation to 0.12-0.13 sec. in 22 patients.

Sex and Age.—This group of 57 patients included 48 males and 9 females, a ratio of 5.4:1, whereas the ratio for patients with normal conduction was 3.7:1. The average age of 59 years for the group was slightly higher than that of 55 years for the patients without conduction defects (Table II).

CLINICAL FEATURES

Incidence of Hypertension and Heart Failure.—Defective intraventricular conduction was usually associated with long-standing hypertension, cardiac enlargement, and congestive heart failure, the respective incidence of each being 77, 84, and 92 per cent, which was definitely higher than in our large control series (Table II). When the QRS interval measured more than 0.15 sec., cardiac enlargement and failure were practically universal.

TABLE II

BUNDLE BRANCH AND INTRAVENTRICULAR BLOCK IN ACUTE CORONARY ARTERY OCCLUSION (375 CASES)

	QRS 0.12-0.13 SEC.	QRS 0.14-0.20 SEC.	TOTAL CASES	NORMAL CONDUCTION (CONTROL GROUP)
No. of cases	22	35	57 (15%)	318
Average age	58.5	59	59	55
Sex: Male	19	29	48 (5.4:1)	3.7:1
Female	3	6	9	
Attacks: 1st	8 (26%)	13 (24%)	21 (35%)	56%
2nd to 4th	14 (64%)	25 (66%)	39 (65%)	44%
Hypertension	17 (77%)	27 (77%)	44 (77%)	62%
Cardiac enlargement	17 (77%)	31 (89%)	48 (84%)	55%
Heart failure	18 (82%)	33 (94%)	51 (92%)	68%
Mortality	6 (27%)	18 (51%)	24 (42%)	23%

Incidence of Previous Attacks.—Defective intraventricular conduction was more common in patients who had sustained previous attacks of coronary occlusion than in patients in their initial attack. Two-thirds of the patients in this group were suffering from a second or later attack, whereas less than half the patients with normal conduction had had a previous occlusion.

The importance of repeated attacks of occlusion in the development of bundle branch block is illustrated by a patient (Case 4) observed during three attacks of coronary occlusion over a period of six years (Fig. 1). Following his first attack the QRS interval measured 0.10 sec., and after the second attack it became prolonged to 0.14 sec. After the third attack it increased to 0.18 sec., and the electrocardiographic pattern changed from left to right bundle branch block. A similar instance was that of a 69-year-old man (Case 15) who was observed clinically during two attacks of coronary occlusion. After the first attack the

QRS became prolonged to 0.12 sec., and the electrocardiogram gradually assumed the appearance of partial bundle branch block. One year later he suffered another occlusion and typical left bundle branch block developed, the QRS measuring 0.15 sec. Necropsy revealed that the first occlusion had involved the left coronary artery, and the second, the right.

Time of Onset.—The conduction defect usually developed soon after the coronary artery occlusion, although the exact time of onset could not be determined accurately in many cases, for few electrocardiograms taken prior to admission to the hospital or prior to the attack were available. In sixteen patients admitted on the first day of the attack

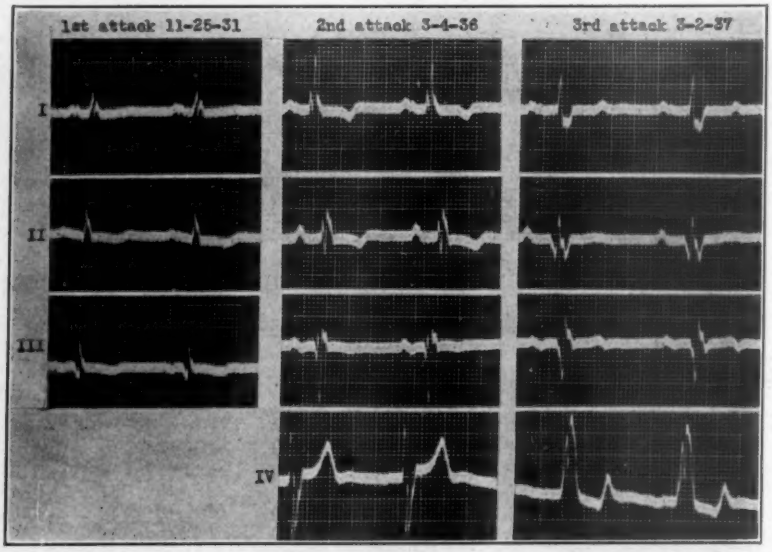

Fig. 1.—Case 4. Male, age 59 years. Effect of repeated attacks of coronary occlusion on intraventricular conduction. The QRS interval increased from 0.10 sec. in the first attack to 0.14 sec. during the second and 0.18 sec. during the third. Simultaneously the P-R interval increased from 0.20 sec. to 0.26 sec. The sudden increase in A-V and intraventricular block in each attack was of great diagnostic significance. The patient recovered.

the intraventricular block was already present. In thirty-two patients who entered at intervals of two to twenty days following the attack the conduction defect was observed in the first electrocardiogram obtained. Five patients (Cases 36, 16, 3, 46, 22) developed intraventricular block while under observation on the 3rd, 10th, 20th, 21st and 39th days, respectively (Figs. 2 and 11). In the four remaining patients (Cases 4, 11, 15, 53), some degree of intraventricular block was present in records taken prior to the last attack in which we treated them. Even in these cases, however, the intraventricular block was related to coronary occlusion; in three it had set in following a previous attack and had increased in degree following the later one (Fig. 1).

Duration.—In marked contrast to auriculoventricular block[39] and other arrhythmias[40] in coronary artery occlusion, intraventricular block was usually permanent. The conduction defect persisted in 23 patients until death, which occurred at intervals of one day to several months following the onset of their attack. In 27 patients who survived, the conduction defect was still present in records taken several months to two years later (Figs. 1, 6, 9). In six patients, however, the intraventricular block was transient and disappeared or diminished in degree within several days or weeks. The transition to normal conduction was sudden in four of these patients (Figs. 3, 4, Cases 6, 33, 41, 57). In one patient with typical left bundle branch block (Case 7) there was gradual lifting of the block; after one week every other beat was con-

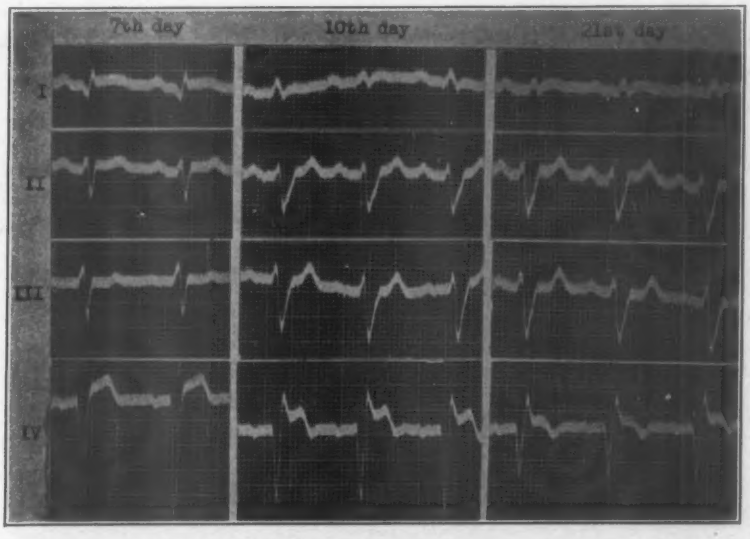

Fig. 2.—Case 11. Male, age 66 years. Sudden appearance of atypical bundle branch block (right?) 10 days after an acute coronary occlusion. The QRS interval is prolonged to 0.15 sec. The typical Q_1 T_1 pattern of anterior wall infarction, present at the onset of the attack, is masked by the conduction defect, except in the precordial lead. The patient died of heart failure during the fourth week.

ducted normally, the conduction defect being present in alternate beats only; it then became more intermittent, appearing only in isolated beats, and finally, after several weeks, there was complete disappearance of the left bundle branch block (Fig. 5).

Symptoms and Physical Signs.—The appearance of bundle branch or intraventricular block did not give rise to specific symptoms. Although severe heart failure was present as a rule, it was attributable to the coronary occlusion and not to the block. It must be kept in mind, however, that complete A-V heart block rarely may result from bilateral bundle branch block[5, 11, 15, 27, 41] and produce an Adams-Stokes syndrome. Thus in Case 26 the sudden onset of syncope and slowing of the pulse to less than 40 was associated with the appearance first of left and then of right

bundle branch block, suggesting that the syncope was due to complete A-V block resulting from involvement of both bundle branches simultaneously.

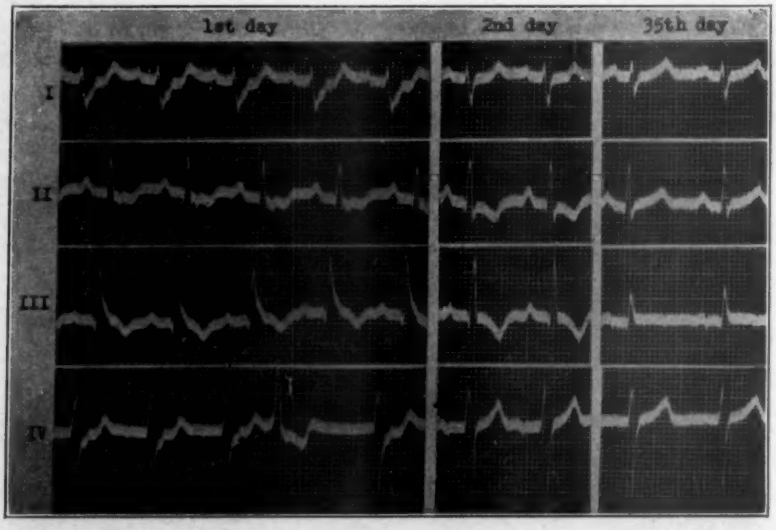

Fig. 3.—Case 33. Female, age 57 years. Transient right bundle branch block on the first day of acute coronary occlusion; the QRS interval is prolonged to 0.14 sec. On the 2nd day there is normal conduction with a T_2 T_3 pattern typical of posterior wall infarction. The electrocardiogram returns to normal on 35th day. The patient recovered.

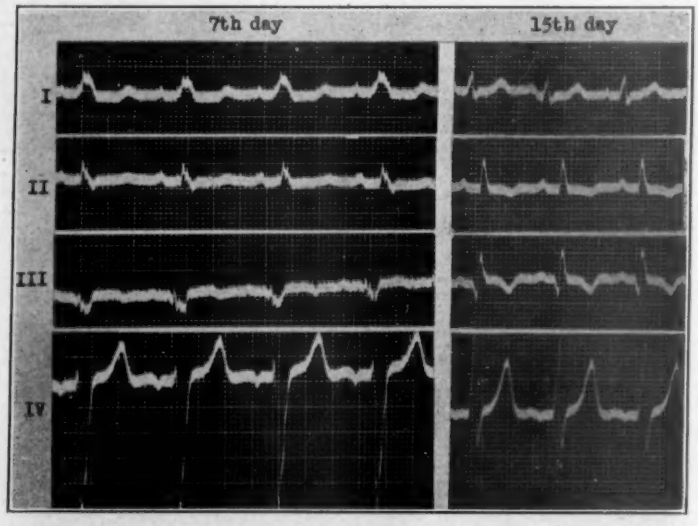

Fig. 4.—Case 6. Male, age 50 years. Transient intraventricular block following coronary artery occlusion, lasting two weeks. The intraventricular block masks the characteristic signs of infarction. With return of normal conduction, the typical Q_3 T_3 pattern of posterior wall infarction appears. The small initial positive deflection in the precordial lead in the first record can be ascribed to the intraventricular block. The patient recovered.

On examination our patients did not present the signs of bundle branch block described by King and McEachern,[42] palpable reduplication of the apical impulse being observed only occasionally and splitting of the first heart sound in only four cases. Although diastolic gallop rhythm was present in 60 per cent of the cases, a higher incidence than existed in a larger series of unselected cases of coronary occlusion previously reported,[43] it was probably associated with the greater frequency and degree of heart failure in the presence of bundle branch block.

ELECTROCARDIOGRAPHIC FEATURES

Types of Block.—Left bundle-branch block of the common type, as evidenced by left axis deviation and widening of the QRS interval to

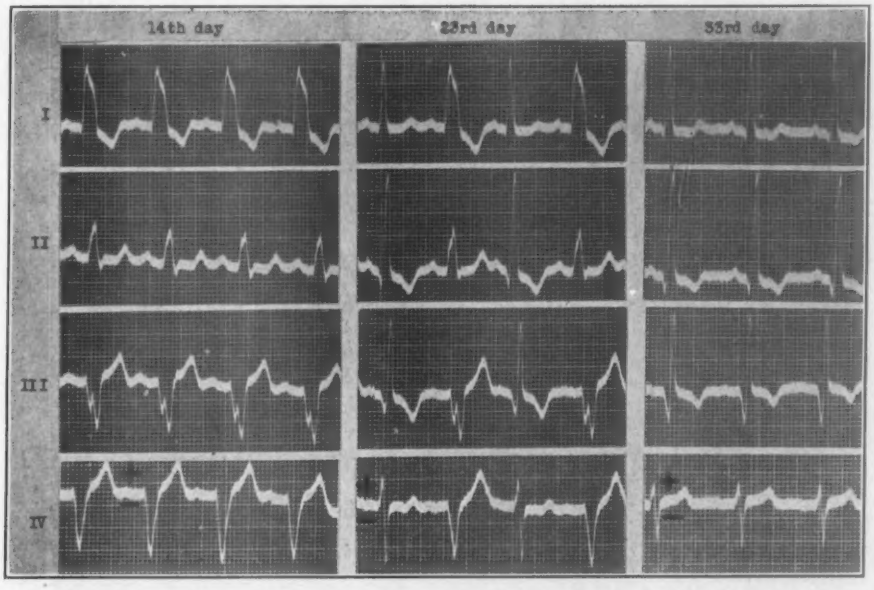

Fig. 5.—Case 7. Female, age 47 years. Transient and intermittent left bundle-branch block following acute coronary occlusion. The bundle branch block is constant until the 4th week, then every alternate beat is conducted normally, resulting in 2:1 bundle branch block. The latter disappears on the 33rd day. The bundle branch block masks the Q_3 T_3 pattern of posterior infarction, present in the normally conducted beats. The initial positive deflection is absent only when bundle branch block is present. The patient recovered.

0.12 sec. or more, occurred 29 times (Fig. 5). Typical right bundle branch block, indicated by right axis deviation and widening of the QRS complex, was observed in seven cases (Fig. 3). In addition there were nine instances of atypical right bundle branch as classified by Wilson and his associates,[44-46] characterized by a large, broad S-wave in Lead I, regardless of axis deviation (Fig. 1). In this type the QRS deflection in Lead I may be very small (Fig. 2). Finally, ten records fulfilled none of the above criteria and were classified as intraventricular block; in some of these the QRS complex was of low voltage (Fig. 4). It is thus seen that right bundle branch block was much more frequent in these

cases of coronary occlusion than had been reported previously in bundle branch block from all causes,[3, 4, 47] but this is due in great part to the new criteria of Wilson. Several records heretofore considered intraventricular block were classified as right bundle branch block.

The Distortion and Variability of Bundle Branch Block.—The bundle branch block pattern following infarction was often distorted by the presence of low voltage, prominent S-T deviations, and variations in the direction of the T-waves. This had already been observed clinically[29] and also experimentally[48] by simultaneous ligation of a coronary artery and cutting of a bundle branch. The myocardial infarction, as well as the location of the bundle branch lesion, is important in determining the electrocardiographic configuration.

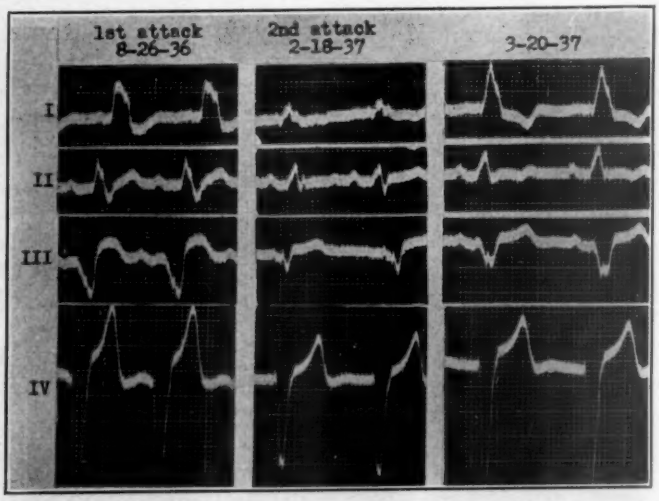

Fig. 6.—Case 2. Female, age 66 years. Variation in configuration of the ventricular complexes in bundle branch block. Following the 1st attack of coronary occlusion typical left bundle branch block developed. After the 2nd attack the ventricular complexes became very low and bizarre, the typical configuration of bundle branch block returning several weeks later. The characteristic signs of infarction are masked by the conduction defect. The patient recovered.

Furthermore, while bundle branch block ordinarily is fixed in appearance, following coronary occlusion it may vary from record to record, as illustrated by Case 2 (Fig. 6) in which typical left bundle branch block was present on admission soon after the attack. Subsequently the ventricular complexes assumed a bizarre form with very low voltage, and finally left bundle branch block returned. Another interesting example was Case 14 in which intraventricular block was present on the day of the attack (Fig. 7). On the third day typical right bundle branch block appeared but was again replaced on the next day by intraventricular block without axis deviation; the patient died on the fifth day, and necropsy revealed massive infarction of the entire interventricular septum.

Not only may the electrocardiographic pattern vary from day to day, but the bundle branch block may shift suddenly from left to right and vice versa. Thus in Case 4 left bundle branch block appeared after the second attack of coronary occlusion and was replaced by atypical right bundle branch block immediately after a third attack (Fig. 1). In Case 26 left bundle branch block on the second day of the attack was followed by right bundle branch block on the third day (Fig. 8).

These variations in the appearance and direction of the ventricular complexes depend upon two factors: first, the extent of the infarction and of the surrounding inflammatory reaction may change rapidly, and, second, the degree of ischemia of the conduction system may vary as a result of variations in the coronary blood flow. A diminution in the latter may produce a transient functional impairment in conduction

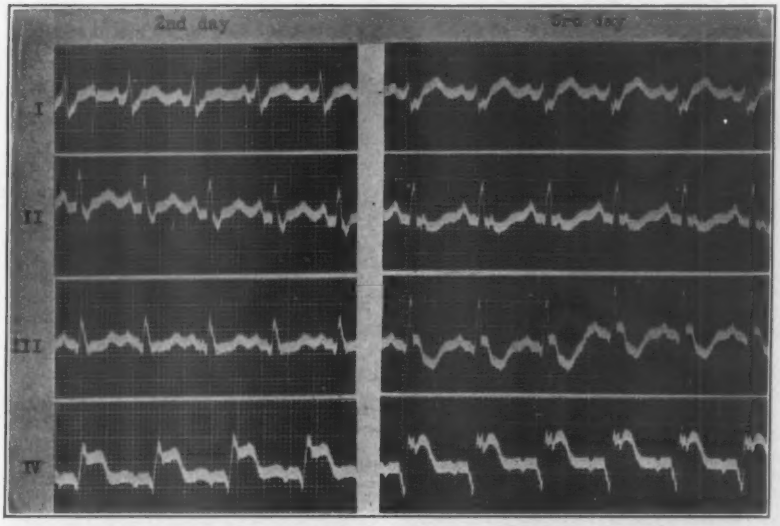

Fig. 7.—Case 14. Male, age 47 years. Intraventricular block on 2nd day (QRS 0.12 sec.) progressing to typical right bundle branch block on 3rd day (QRS 0.15 sec.). The precordial lead is characteristic of anterior wall infarction. Death occurred from cerebral embolism on 5th day. Autopsy showed infarction of the anterior and posterior surfaces of the heart and massive infarction of the entire interventricular septum, due to acute occlusions of both the left and right coronary arteries.

outside the infarcted area, resulting in the bizarre electrocardiographic pattern of interventricular block. Of considerable importance in this respect is the effect of tachycardia, which increases the degree of ischemia already present, and leads to functional fatigue of the conduction system. Electrocardiographically this often resulted in very marked alterations in the ventricular complexes which disappeared when the tachycardia ceased (Figs. 8 and 9).

Electrocardiographic Signs of Infarction in the Presence of Bundle Branch Block.—Serial changes in the S-T interval and T-wave permitted a diagnosis of acute infarction in two-thirds of the cases. Nineteen cases presented the T_1 pattern associated with anterior wall infarction and

nine the T_3 pattern of posterior infarction; in ten there were changes in all three standard leads suggesting both anterior and posterior infarction. This electrocardiographic localization was confirmed at autopsy in most

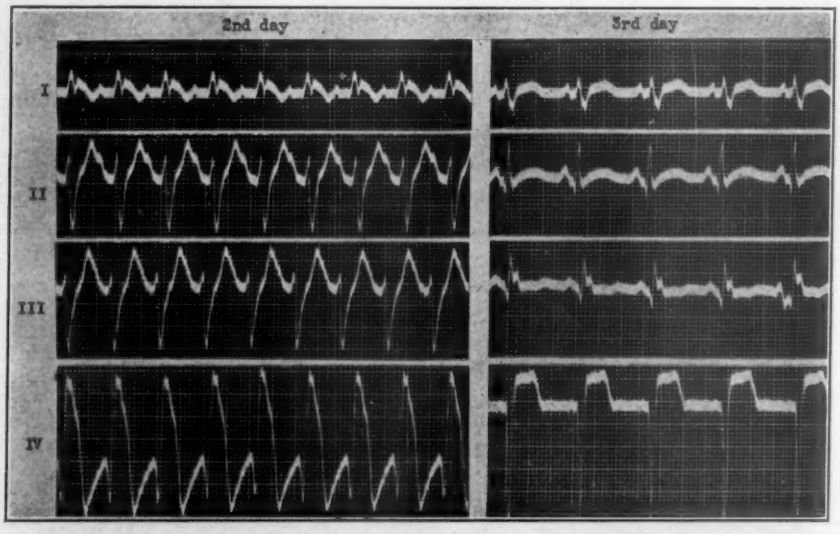

Fig. 8.—Case 26. Male, age 35 years. Transient atypical left bundle branch block associated with auricular paroxysmal tachycardia, followed by permanent right bundle branch block. The record, particularly the precordial lead, is characteristic of acute anterior wall infarction. The patient recovered.

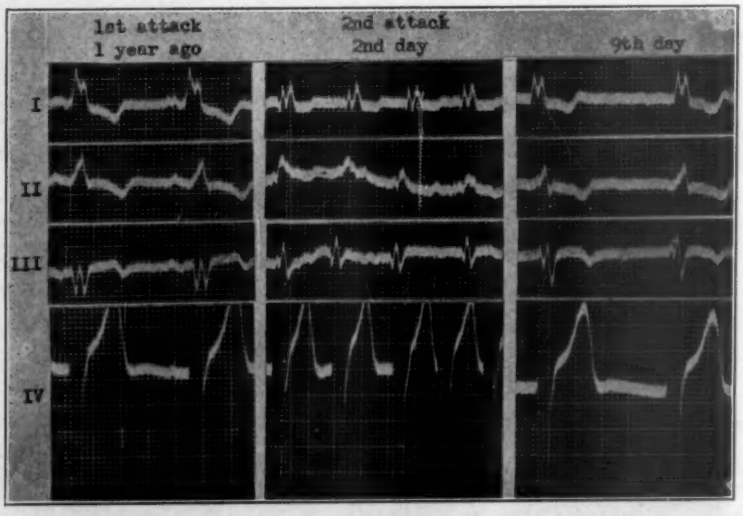

Fig. 9.—Case 11. Male, age 67 years. Effect of tachycardia on bundle branch block. Permanent left bundle branch block developed following 1st attack of coronary one year before. Sudden onset of auricular fibrillation with rapid ventricular rate following 2nd attack. The ventricular complexes become distorted and resemble those seen in intraventricular block. Following slowing of the ventricular rate by digitalis, the complexes reassume the characteristic configuration of left bundle branch block. The patient recovered.

cases, although in a few instances the electrocardiogram was of the T_1 or T_3 type alone, and autopsy examination showed infarction of both surfaces.

In nineteen, or one-third, of the patients, the bundle branch block masked the electrocardiographic signs of myocardial infarction, that is, characteristic progressive changes in the S-T interval and T-wave failed to appear. This observation has also been made by other authors.[18, 29, 49-51] The more marked the intraventricular conduction defect, the less often did the typical changes of infarction appear. Thus in all but one of these cases the QRS interval measured at least 0.14 sec. Since the classical clinical signs of coronary occlusion were usually present, the diagnosis was rarely in doubt despite the absence of characteristic electrocardiographic changes. Even in cases of this type serial electro-

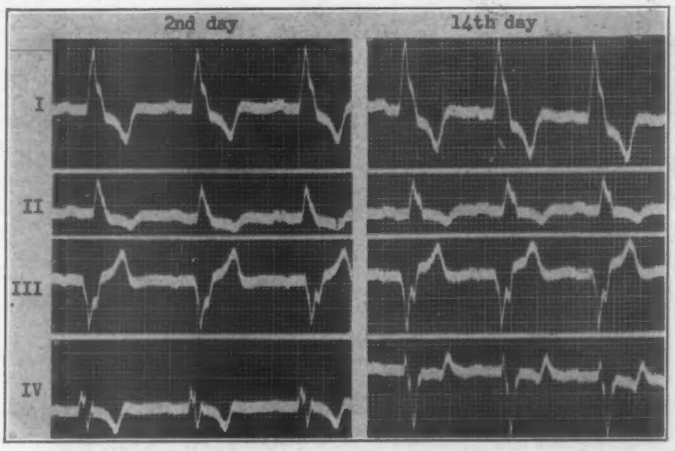

Fig. 10.—Case 13. Female, age 57 years. Typical left bundle branch block following 2nd attack of coronary occlusion. The conduction defect masks the signs of infarction in the standard leads, but progressive changes in the T-wave are observed in the precordial lead. The patient recovered.

cardiograms may be useful, for the bundle branch block may remit and changes characteristic of infarction may then appear (Figs. 4 and 5).

The Precordial Lead in the Presence of Bundle Branch Block.—Unlike the standard leads, the precordial lead may be of diagnostic aid in the presence of bundle branch block, for characteristic progressive S-T and T-wave changes may appear in this lead alone (Figs. 10 and 11).

We have elsewhere[54] discussed the importance of an absent or very small initial positive deflection in the precordial lead in the diagnosis of coronary occlusion with anterior wall infarction. However, other authors[17, 55, 56] as well as we have pointed out that this deflection is occasionally absent and frequently very small in bundle branch block not associated with myocardial infarction, a fact illustrated by Cases 6 and 7. In both of these cases with posterior wall infarction this deflection returned to normal when the bundle branch block disappeared (Figs. 4

and 5). Nevertheless, certain observations suggest that in many cases of bundle branch block the absent or small initial deflection is produced by anterior wall infarction. In 23 out of 27 cases with bundle branch block, the absent or very small initial deflection could be explained in this way, for the electrocardiogram was of the T_1 or $T_{1, 2, 3}$ pattern of anterior or both anterior and posterior infarction. Furthermore, post-mortem examination in 12 cases revealed infarction of the anterior wall in 11 cases, and infarction limited to the posterior wall in one, whereas in the entire series the incidence of anterior and posterior infarction was the same. Hence in most cases the abnormal initial positive deflection may be considered a presumptive sign of infarction of the anterior wall even

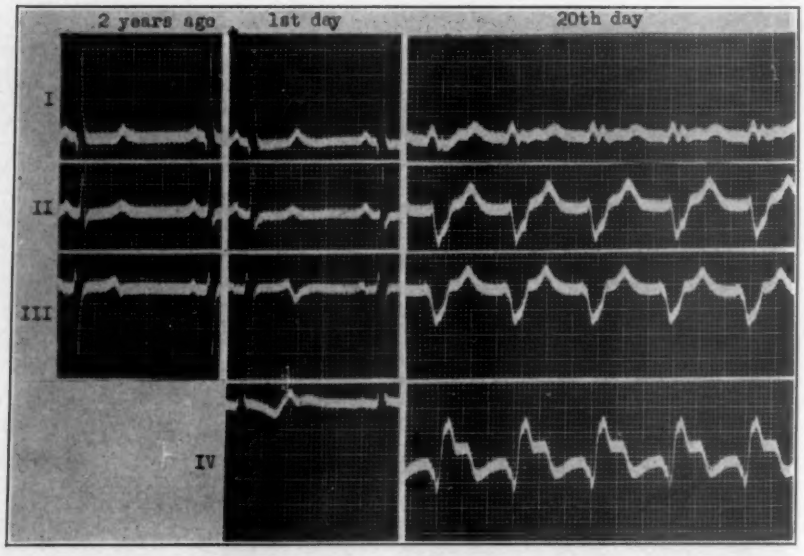

Fig. 11.—Case 3. Male, age 72 years. Sudden onset of atypical bundle branch block (right?) on the 20th day of attack, associated with idioventricular rhythm, rate 95. The precordial lead is characteristic of anterior wall infarction. There was a concomitant recurrence of precordial pain and shock, increase in heart failure, and appearance of a harsh systolic murmur and thrill suggestive of septal perforation, verified at autopsy. There was massive infarction of the septum with perforation, and infarction of the anterior wall of the left ventricle, due to occlusion of the left anterior descending artery.

when bundle branch block is present, although occasionally the latter alone is the cause.

Association of Bundle Branch Block With A-V Block and Other Arrhythmias.—Disturbances in intraventricular conduction were frequently associated with defective A-V conduction. Thus the P-R interval was prolonged to 0.20 sec. or more in 20 patients, an incidence twice as high as in patients with normal conduction[39]; in 7 patients it ranged from 0.24 to 0.40 sec. (Fig. 1). Complete heart block occurred in 3 cases (17, 14, 53). The association of bundle branch block with impaired A-V conduction received early emphasis in the literature.[2, 52] In several large series[3, 4, 36] of unselected cases of bundle branch and intraventricu-

lar block, the incidence of heart block ranged from 9 to 23 per cent. It is also noteworthy that in 13 of 15 cases of heart block following acute coronary occlusion described by Schwartz[50] there was, in addition, intraventricular block. These observations and our own suggest that the underlying cause for both A-V and intraventricular block in coronary artery occlusion is the same, i.e., occlusion of the specific arteries to the septum with infarction of the region of the A-V bundle and its branches. The septal infarct which we believe to be the cause of the bundle branch block may either extend high enough to involve the A-V node or bundle, or, as suggested previously,[5, 27] the infarct may involve both bundle branches simultaneously and thus produce defective A-V conduction.

Other arrhythmias were associated with bundle branch block no more often than with coronary artery occlusion in general.[40] The arrhythmias encountered, in addition to premature beats, were auricular fibrillation, 3 (Fig. 9); paroxysmal auricular or nodal tachycardia, 4 (Fig. 8); and ventricular tachycardia, 2 (Fig. 11). Special emphasis has been placed by many authors on the latter as a complication of coronary artery occlusion,[40] and it is interesting that several[27, 34, 53] have ascribed this arrhythmia to an infarct in the septum, the same lesion underlying bundle branch block. Yet in the 375 cases studied, only four instances of ventricular tachycardia were encountered, despite the frequency of septal infarction, and only two were associated with bundle branch or intraventricular block. In one of these cases examined post mortem (Case 3), the ventricular tachycardia and bundle branch block were found to be associated with massive septal infarction and septal perforation, suggesting that the view of the above authors may hold true in some cases.

DIAGNOSTIC SIGNIFICANCE

Diagnostic Significance of Bundle Branch Block in Acute Coronary Occlusion.—The sudden appearance of defective intraventricular conduction, transient or permanent, should suggest the possibility of recent coronary artery occlusion, even when typical clinical or electrocardiographic signs are lacking, particularly when associated with the onset of shock or heart failure. For example, one patient (Case 4) was observed in three attacks of pulmonary edema during six years, each attack associated with sudden prolongation of the QRS interval, and the third with a shift from left to right bundle branch block (Fig. 1). Because of these changes coronary occlusion was suspected each time and confirmed later by clinical observation. Similarly, in Case 7 the symptoms at first suggested acute cholecystitis, but coronary occlusion was suspected when bundle branch block was observed in the electrocardiogram (Fig. 5). This was corroborated when typical electrocardiographic changes became evident following the disappearance of the conduction defect. Furthermore, another occlusion or extension of the infarction should be suspected when bundle branch or intraventricular block suddenly develops several

days or weeks after an occlusion. Of five such cases, the onset of the bundle branch block was associated with a recurrence of precordial pain and shock in four, and post-mortem confirmation of another occlusion was obtained in the two cases in which an autopsy was performed (Cases 3 and 46).

Relation of Coronary Occlusion to Permanent Bundle Branch Block.—Since bundle branch or intraventricular block may become permanent following coronary occlusion, it may be the only electrocardiographic evidence that the patient has suffered a coronary occlusion in the past.[34] Thus 10.8 per cent of 576 cases of bundle branch and intraventricular block from all causes[3, 36] were associated with a known previous coronary artery occlusion. In a smaller series of bundle branch block cases studied by us,[57] 16.5 per cent followed acute coronary artery occlusion.

PROGNOSTIC FEATURES

The presence of bundle branch or marked intraventricular block adds to the seriousness of acute coronary artery occlusion, being associated with a mortality rate of 42 per cent as compared to 23 per cent in patients with normal conduction (Table II). The course of the illness in such patients is severe because of the greater degree of congestive failure and cardiac enlargement. Not only is the coronary artery sclerosis usually advanced, but at necropsy evidence of previous closure of one or more coronary arteries is almost universal. As a rule the increase in mortality and the severe heart failure occurred in the cases in which the QRS interval measured 0.14 sec. or more. Only occasionally was bundle branch block present without evidence of cardiac failure or enlargement (Table I). The mortality rate and incidence of heart failure were not influenced by the type of conduction defect, being the same whether left or right bundle branch block or intraventricular block was present.[3]

POST-MORTEM OBSERVATIONS

Site of Occlusion.—Necropsy, performed in 20 cases, revealed that the incidence of defective intraventricular conduction was the same whether the right or the left coronary artery was occluded. A recent occlusion was present in the left coronary artery in 7 cases, in the right in 5 cases, and in both arteries in the remaining 8. In addition, one or more arteries had been previously occluded in 16 of the 20 hearts, explaining the extensive myocardial damage usually observed.

Site of Infarction.—As one would expect from the foregoing figures, acute infarction of the anterior and posterior walls occurred with equal frequency. The anterior surface was involved in 6 cases, the posterior surface in 6 cases, and both surfaces simultaneously in the remaining 8.

The most consistent finding at necropsy was infarction of the interventricular septum, which was present in four-fifths of the cases. When the QRS interval measured more than 0.14 sec. infarction of the septum

was practically universal, whereas in patients with normal intraventricular conduction it occurred in only half the cases.[1] Furthermore, the incidence of defective conduction in 30 hearts with septal infarction was 43 per cent, while in 19 hearts in which the infarction spared the septum it was only 21 per cent. It appears, therefore, that the presence of septal infarction following acute coronary artery occlusion doubles the frequency of bundle branch or intraventricular block.

Cardiac Enlargement.—Intraventricular or bundle branch block was usually associated with considerable cardiac enlargement. The cardiac weight ranged from 400 to 490 gm. in seven cases, from 500 to 590 gm. in ten cases, and was 730 gm. in the remaining case, the average being 505 gm. In comparison, the average cardiac weight was only 440 gm. in 30 patients with normal intraventricular conduction who died of coronary occlusion; one-third of these hearts weighed less than 400 gm. The relation of cardiac enlargement to the pathogenesis of bundle branch block will be discussed below.

PATHOGENESIS OF BUNDLE BRANCH BLOCK

Anatomical Basis.—Since the main bundle branches run within the interventricular septum, one would expect bundle branch block to result from injury to this region. In animals septal infarction produced by ligation of the septal artery results in bundle branch block,[41, 51, 58-61] with few exceptions.[34, 62] In our series septal infarction was found in four-fifths of the cases. When the QRS interval was 0.14 sec. or more, septal infarction was constant. The obstruction to conduction is probably situated high up in the septum in the main bundle branches or their larger subdivisions. This would explain the frequency of associated disturbances in A-V conduction since these would be likely to occur when the infarct extended high enough to involve the A-V node or bundle. In mild degrees of intraventricular block the lesion may be lower down near the apex[2, 47] or in the subendocardial Purkinje system, despite the objection[29, 62-67] that the latter is resistant to ischemia. This would account for the absence of gross septal infarction in one-fifth of the cases with some degree of intraventricular block. However, it is not unlikely that minute study of the septum and bundle branches would have revealed some damage, or the block may have been the result of other factors such as anoxemia, as will be discussed later.

Normal Intraventricular Conduction with Septal Infarction.—Although high-grade intraventricular and bundle branch block were associated as a rule with septal infarction, the latter may be extensive and yet conduction may remain normal. Thus in only two-fifths of 30 cases with gross septal infarction studied previously[1] was there impaired intraventricular conduction, and other authors have described similar cases.[63, 68] Gross[64] offered two possible explanations. First, the specific blood supply to the conduction system may not be involved, despite closure of the main coronary vessels, for the occlusion may occur distal

to the origin of the septal branches.[36] Second, the anastomosis between the left and right coronary arteries in the septum may be so profuse that, when occlusion of one artery occurs, anastomotic channels from the patent vessel maintain an adequate circulation to the conduction system. Most of the anatomical and experimental evidence[62, 69-73] supports this view, although Mahaim[27] believes that there are few anastomotic vessels in the septum.

Correlation of Site of Occlusion and Type of Bundle Branch Block.—Since the right bundle branch is supplied almost exclusively by the septal branch of the left anterior descending artery, right bundle branch block should result from occlusion of this artery.[63, 64, 68, 73] Similarly, both the left and right coronary arteries theoretically should be occluded to produce left bundle branch block, for the left bundle is supplied by both vessels. Intraventricular block should be more common with left coronary occlusion, since this vessel provides the greater part of the blood supply to the ramifications of both bundle branches. Several authors[27, 30, 74] have utilized these anatomical observations in the attempt to localize the site of occlusion or infarction from the type of conduction defect. We agree with others[28, 50] that this cannot be done accurately, for our autopsy material fails to show agreement between the theoretical expectations and the actual vessels occluded. Occlusion of the right coronary artery was as frequent as that of the left, irrespective of the existing type of bundle branch block. Furthermore, multiple acute and old occlusions were usually present, so that it was very difficult to determine which occlusion was the cause of the conduction defect. Similarly, no correlation could be made between the type of conduction defect and anterior or posterior wall infarction. It is evident, however, that in our experience right coronary artery occlusion led to bundle branch block of either type more often than was to be expected from the distribution of the blood supply to the conduction system.

Transient Bundle Branch Block.—Anoxemia: Although infarction of the interventricular septum is the usual basis for bundle branch or intraventricular block in coronary artery occlusion, we have seen that in a few cases the conduction defect was transient and that occasionally septal infarction was not found at necropsy. In these the block may have been functional in nature, induced by anoxemia of the conduction system. The influence of anoxemia on conduction through the bundle branches and their ramifications is still a matter of dispute, the conduction system being found resistant by some investigators[65-67] and sensitive by others.[7, 75-79] It is noteworthy that transient bundle branch block has been observed during an attack of angina pectoris,[80, 81] suggesting that myocardial ischemia may result in functional fatigue of the conduction system.

In coronary occlusion several factors may lead to fatigue of the conduction system in the absence of septal infarction. As a result of shock

and drop in blood pressure, the cardiac output, and therefore the coronary circulation, are reduced. Robinson and Auer[82] attributed to coronary insufficiency the bundle branch block occurring in animals after the induction of anaphylactic shock. The effect of diminished cardiac output on coronary flow is enhanced by the heart failure which is very common in cases with bundle branch block. Transient bundle branch block has not infrequently been observed in congestive heart failure without occlusion.[7, 22, 76-78, 83-85] Two of our six cases of transient bundle branch block occurred in patients with severe failure; one was associated with severe shock. Finally, tachycardia may further burden a coronary circulation already impaired by occlusion and so induce bundle branch block which disappears with the cessation of the rapid rate.[76, 77, 86, 87] In Case 26 transient left bundle branch block appeared during a paroxysm of auricular tachycardia (Fig. 8), and in Cases 5 and 40 the duration of the QRS interval was temporarily increased. In other instances of tachycardia, however, there was normal intraventricular conduction.

Bundle branch block may be transient even when septal infarction is present. The inflammatory reaction and edema surrounding the infarct may diminish after several days, and the bundle branches involved by this process may regain their conductivity. Similarly, collateral circulation from the other coronary artery may establish itself and restore normal conduction. Of interest in this regard are the clinical observations made in Case 7, in which the bundle branch block was abolished temporarily by the intravenous injection of aminophyllin, probably as a result of transient dilatation of the surrounding patent coronary vessels, with improvement in circulation to the conduction system. When collateral circulation was permanently improved within a few weeks, the bundle branch block disappeared spontaneously.

The Effect of the Vagus on Intraventricular Conduction.—Auriculoventricular conduction disturbances due to vagal influences are observed frequently. Whether the latter may also affect conduction through the bundle branches is not entirely clear. Although functional bundle branch block due to vagal stimulation has been reported,[5, 7, 88] it has been stated[89] that intraventricular conduction is not influenced by the vagus nerve. The circulatory factors in coronary occlusion are so evident that vagal stimulation need not be invoked as an explanation for the production of bundle branch block even when the latter is only transient. Were the vagus nerve important, abolishing its action with atropin should decrease the conduction defect. In three cases in which 1/50 gr. of atropin was administered intravenously, the conduction defect was unaffected although the P-R interval was definitely shortened.

The Importance of Cardiac Enlargement in Bundle Branch Block.—We have seen that cardiac hypertrophy was present in every autopsy case with intraventricular block, the majority of hearts weighing 500 gm. or more, and the average weight being 505 gm. Furthermore, we

have found[57] the degree of cardiac enlargement in bundle branch block without myocardial infarction to be even more marked, the average cardiac weight being 660 gm. This suggests a relationship between cardiac enlargement and bundle branch block, particularly since in a large heart without a bundle branch lesion the electrocardiographic configuration not infrequently approaches that of bundle branch block. In coronary occlusion, however, bundle branch block would seem to depend chiefly on the presence of septal infarction. Thus large hearts were observed without conduction defects and, conversely, bundle branch block occurred occasionally when there was little enlargement (Table I). Furthermore, were heart size a factor, one would expect left bundle branch block almost exclusively to have occurred, because of the high incidence of antecedent hypertension and left ventricular enlargement; yet in our series right bundle branch block was frequent. Nevertheless, it may be that a large heart predisposes to the development of bundle branch block in the presence of myocardial infarction or ischemia.

Involvement of a bundle branch usually influences the electrocardiogram differently than cardiac enlargement. Marked widening, notching and slurring of the QRS, with high voltage, seem to be caused by the former, whereas high voltage without widening may result from enlargement alone.

TREATMENT

The treatment of coronary artery occlusion with bundle branch or marked intraventricular block does not differ from the treatment of coronary occlusion in general. Our regime has been described in detail in previous publications,[43, 90, 91] and consists essentially of complete physical and mental rest, good nursing, prevention of gastrocardiac reflexes and lowering of the body metabolism by a low caloric diet, and sufficient sedatives and analgesics to control apprehension and pain. The therapy of congestive heart failure is especially important because of its high incidence in the cases with bundle branch block and because the failure may increase the anoxemia of the conduction system. Emphasis is to be placed on such measures as diminished fluid intake, low calory diet, oxygen administration and mercurial diuretic drugs in conjunction with acidifying salts. Oxygen therapy, particularly, has been found beneficial for defective intraventricular conduction associated with tachycardia[86] and heart failure.[83]

We avoid the use of digitalis in coronary artery occlusion, particularly early in the attack, even when congestive heart failure is present, for we believe that in the presence of acute infarction it may be toxic in ordinary therapeutic doses.[40, 91] We resort to its use only when other measures for the treatment of heart failure have failed.

Quinidine sulphate has been advocated in coronary occlusion to prevent ventricular tachycardia. Septal infarction, which has been shown

to be the underlying pathologic basis for bundle branch block, has also been thought to be the cause of ventricular tachycardia.[27, 34, 53] The septal infarction may either block conduction through the bundle branches or set up an irritative focus leading to ventricular tachycardia. Theoretically, therefore, quinidine would be indicated in cases of coronary artery occlusion with bundle branch block as a prophylactic measure against ventricular tachycardia. Practically these considerations do not hold true, for as we have seen previously, in only 2 of our 56 cases was there ventricular tachycardia, and only four instances of the latter were observed in the 375 cases of coronary occlusion.[40] Such a small incidence does not warrant the routine prophylactic administration of quinidine. Furthermore, experimental studies[92-94] have shown that quinidine in therapeutic doses depresses intraventricular conduction and in toxic doses may cause marked intraventricular block. Clinically, also, cases of bundle branch block following quinidine administration have been observed.[95-97] It is possible, therefore, that the use of quinidine in the presence of bundle branch block or intraventricular block may actually increase the degree of conduction defect.

A drug which should be used more frequently in the acute stage of coronary artery occlusion is aminophyllin, administered intravenously. Its use in two of our patients deserves special mention. In Case 26, it was a life-saving measure. The patient, a 35-year-old man, suddenly became unconscious on the second day of his attack. The heart rate first slowed to 40 per minute, and then the heart beats became entirely inaudible, and the patient appeared dead. The intravenous injection of 0.24 gm. of aminophyllin at this point caused a sudden revival of the patient. Following a transient seizure of auricular tachycardia with left bundle branch block, permanent right bundle branch block appeared (Fig. 8). The patient recovered and is alive and well today. The presence of both left and right bundle branch block in rapid succession suggests that a possible cause of the syncope was an Adams-Stokes seizure due to bilateral bundle branch block, which was lifted by the transient improvement in coronary blood flow following the injection of aminophyllin. In Case 7 we were successful in abolishing left bundle branch block temporarily by the intravenous injection of this drug. By improving the collateral circulation to the infarct and the area surrounding it, aminophyllin may hasten the return of normal conduction in the transient types of bundle branch block following coronary artery occlusion.

SUMMARY

1. Intraventricular block, including bundle branch block, was present in 15 per cent of 375 cases of acute coronary artery occlusion.

2. Patients in this group were older than controls and presented clinical and pathologic evidence of severe heart disease. Congestive

heart failure, antecedent hypertension, cardiac enlargement and evidence of previous attacks were the rule.

3. The conduction defect was usually observed on the first day and was usually permanent. In six patients it was transient.

4. Intraventricular or bundle branch block could not be diagnosed clinically since there were no specific symptoms or physical signs. Gallop rhythm was present in 60 per cent of the cases, but was probably due to the associated severe heart failure.

5. Left bundle branch block occurred in 51 per cent of the group, typical or atypical right bundle branch block in 28 per cent and intraventricular block in 21 per cent. The configuration of the ventricular complexes as well as the axis deviation often varied in serial records.

6. In the presence of intraventricular block characteristic electrocardiographic signs of myocardial infarction failed to appear in one-third of the cases.

7. The precordial lead may be of diagnostic importance, for progressive S-T and T-wave changes may occur only in this lead. Absence or marked diminution in the initial positive deflection in this lead is usually due to anterior wall infarction even when bundle branch block is present, although occasionally the latter alone is the cause.

8. Intraventricular block was often associated with impaired auriculoventricular conduction. Other arrhythmias were not more common than in coronary occlusion in general.

9. The sudden appearance of defective intraventricular conduction should suggest recent coronary occlusion. Since bundle branch or intraventricular block following coronary occlusion is usually permanent, it may be the only evidence that the patient has suffered a coronary occlusion in the past. Repeated attacks of coronary occlusion may result in a progressive increase in the QRS duration.

10. The presence of defective intraventricular conduction in coronary occlusion adds to the seriousness of the prognosis, the mortality rate being 42 per cent. The more severe the conduction defect was, the higher the mortality rate, but there was no correlation with the type of block.

11. The anatomical basis for the conduction defect was septal infarction, which was present in four-fifths of the hearts.

12. Correlation between the vessels occluded or the location of the septal infarct and the type of conduction defect could not be made; occlusion of the right coronary artery was as frequent as that of the left and anterior infarction was as common as posterior infarction, regardless of the type of block.

13. The persistence of normal conduction in many cases with septal infarction was attributed mainly to the presence of adequate collateral circulation in the septum.

14. Transient bundle branch block was probably due to anoxemia resulting from shock, tachycardia, and heart failure.

15. The vagus nerve probably played no role in bundle branch block since the latter was not affected by the injection of atropine.

16. The relation between cardiac enlargement and bundle branch block was discussed, and the influence on the electrocardiogram of cardiac enlargement and bundle branch involvement contrasted.

17. The treatment is that of coronary occlusion in general, with special attention to heart failure. The value of aminophyllin and oxygen was emphasized. Quinidine and digitalis should be used only when there is persistent rapid ventricular rate with failure.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

V. The Later Effects Produced by Ligation of the Right Coronary Artery†

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PREVIOUS articles of this series have dealt with the form of the ventricular complex in direct and semidirect leads from the epicardial surface of infarcts produced by ligation of the anterior descending branch of the left coronary artery.[2-4] This procedure leads to massive infarction of the anterior wall of the left ventricle. As a rule those portions of the anterior wall of the right ventricle which are close to the septum are involved to some extent, but here the infarction is usually patchy, and the boundaries of the areas affected are not as a rule clearly discernible. In order to determine whether direct and semidirect leads from the surface of right ventricular infarcts yield curves similar to those obtained from the surface of left ventricular infarcts, it was, therefore, necessary to study infarcts of the kind produced by ligation of the right coronary artery. These infarcts are confined to the wall of the right ventricle and are as a rule large, conspicuous, and sharply outlined. It is the purpose of this article to describe the observations made upon infarcts of this type.

As in the experiments described in earlier articles, the ligation was performed under aseptic conditions, and the chest wall was completely restored. If the animal survived this initial operation, an electrocardiographic study was made at a later date, when the chest was reopened and the anterior surface of the heart was explored by means of direct and semidirect leads. These leads were taken with a vacuum tube in the string-galvanometer circuit, and the connections were so made that negativity of the exploring electrode produced an upward deflection in the finished record. For direct leads the galvanometer sensitivity was reduced to one-twentieth normal; for semidirect leads it was reduced to three-twentieths normal. Standard Lead I was recorded simultaneously with these special leads and is represented by the upper trace in all of the curves reproduced. Two kinds of exploring electrodes were employed. For ordinary epicardial leads we used a soft-tipped electrode of the type described in a previous article.[5] For leads from the ventricular cavities and for the purpose of determining whether the subepicardial

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†For previous articles of this series see Wilson, Hill, and Johnston[1-3] and Johnston, Hill, and Wilson.[4] The observations reported in this article were briefly described in a paper read at a meeting of the Association of American Physicians.[5] See also Wilson et al.[6-8]

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muscle in a given region was living or dead we made use of a short length of enameled copper wire sharpened at one end where the insulation was scraped off for a distance of 1 or 2 mm. The nature of the curves obtained from living and from dead muscle when such an electrode is employed has been discussed elsewhere.[3, 4, 8] The exploring electrode was paired with an electrode of similar construction in contact with the subcutaneous tissues of the left hindleg.

Ligation of the right coronary artery in the dog seems somewhat less likely to prove immediately fatal than ligation of the anterior descending branch of the left. In the seven experiments which we performed, the ligatures were placed about that part of the vessel which lies close to the junction of the right auricular appendage with the main body of the right auricle. One animal died about one hour after the ligatures were tied. In three instances the ligatures were improperly placed and the main stem of the artery was not occluded. In two of these experiments small infarcts, due to obstruction of one of its branches, were produced. The three remaining ligations were entirely successful, and large infarcts resulted, but one animal died when the chest was reopened at the time of the second operation, so that the electrocardiographic study could not be completed.

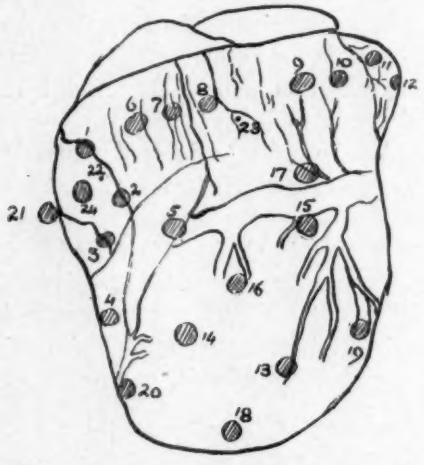

Fig. 1.—Experiment 1 (Dog 38). Outline drawing of the anterior surface of the heart showing the location of the points from which direct leads were taken.

ILLUSTRATIVE EXPERIMENTS

Experiment 1 (Dog 38).—In this instance the electrocardiographic studies were made five days after ligation of the right coronary artery. The standard electrocardiogram taken before the chest was opened shows no Q deflections in any lead but is not unusual in other respects. Three precordial leads were taken. For this purpose small copper disks were sewed beneath the skin along a line extending from the right upper to the left lower part of the precordial region. This line crossed the mid-sternal line 12 cm. below the episternal notch. The first disk was 6.5 cm. to the right of the midline, the second in the midline, and the third 7.5 cm. to the left of the midline. Each disk was paired in turn with a similar disk fastened beneath the skin of the left hindleg. In the first of these precordial curves the QRS complex shows no trace of an

initial downward deflection and closely resembles the initial ventricular deflections recorded in direct leads from the infarcted region. The other two curves display a conspicuous deflection of this kind and are not abnormal.

When the heart was exposed, a trapezoidal area of infarction involving the right anterolateral wall of the right ventricle was clearly visible.

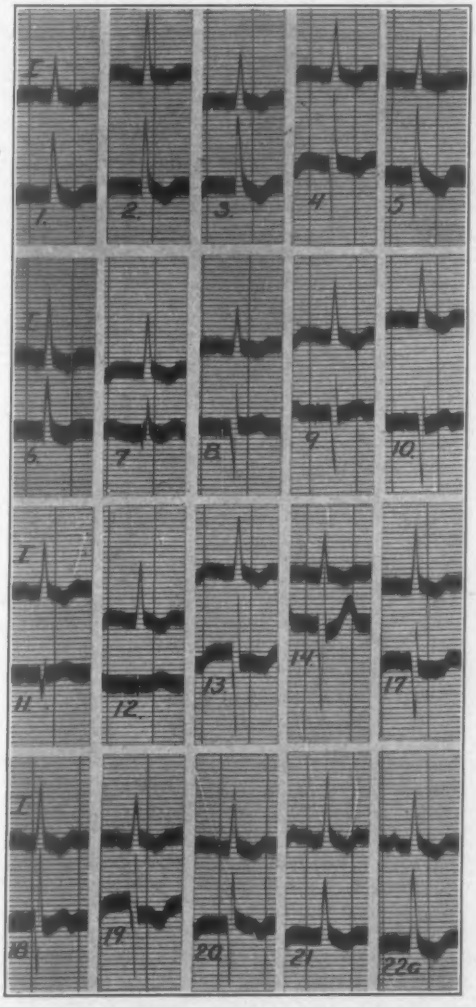

Fig. 2.—Experiment 1 (Dog 38). Direct leads from points marked with corresponding numbers in Fig. 1. The letter *C* indicates that a sharp electrode was employed and was pushed through the ventricular wall so that its uninsulated point was in the ventricular cavity. The upper curve in all records is standard Lead I. In the direct leads relative negativity of the exploring electrode is represented by an upward deflection, and a deflection of 1 cm. represents a potential difference of 20 mv.

The points from which direct leads were taken are indicated on an outline drawing of the heart reproduced in Fig. 1. Many of the curves obtained are shown in Fig. 2. The curves from points 4, 5, 8, 9, 10, 11,

13, 14, 15, 16, 17, 18, 19, and 20, which were outside the boundaries of the infarcted region, all show a prominent initial downward deflection followed by a sharp intrinsic upstroke. Two of these curves, those from points 15 and 16, show definite downward displacement of the RS-T junction indicating very recent injury to the muscle. We attribute this injury to the pressure exerted by the exploring electrode upon the superficial layers of muscle. Accidental disturbances of this kind are frequent when a small electrode is pressed against the beating heart. The deflections of the lead from point 12 are extremely small, apparently because this point lay beyond the pulmonary valves and was not upon cardiac muscle.

In the curves from points 1 and 21 the ventricular complexes consist of a single large upright spike followed by a small U-shaped T deflection and are similar in every respect to those obtained from the surface of left ventricular infarcts which extended completely through the heart wall.[2, 3] The curves from points 2 and 3 differ in one respect only; they show a mere trace of an initial downward deflection. In the curve from point 6 this downward movement is somewhat larger. These points were definitely within the boundaries of the infarcted region. The curve from point 7, which lay very close to the margin of the infarct, may be compared with that from point 8, which was nearby but upon healthy muscle. In the latter there is a deep initial downward deflection followed by an intrinsic deflection of large amplitude; in the former both the initial downward movement and the intrinsic deflection are small, and the intrinsic upstroke is conspicuously notched. The curve obtained by thrusting a sharp electrode through the ventricular wall at point 22 is hardly distinguishable from those obtained from the surface of the infarct at points 1 and 21. The same may be said of the curve recorded when the stab electrode was thrust through the ventricular wall at point 23.

After the curves which have been described had been taken, we attempted to cut the right branch of the bundle of His. This structure was injured but not completely severed, and partial bundle branch block resulted. Standard Leads I and III taken immediately after the cut was made are shown in Fig. 3 *A*. It will be noted that in this tracing ventricular complexes depicting right branch block alternate with complexes of more normal outline. Later the injured bundle passed only an occasional impulse (Fig. 3 *B*). The curve obtained at this time by leading from the epicardial surface at point 24 with a soft-tipped electrode (Fig. 3 *B*) and that obtained by leading from the ventricular cavity at point 22 with the stab electrode (3 *C*) are indistinguishable. It should be emphasized that in both these curves the branch block complexes begin with a large downward deflection, which we attribute to electrical forces generated by the excitatory process in its spread through

the ventricular septum from left to right. The initial deflection of the QRS complexes inscribed when the right bundle branch functioned in the normal way is in the upward or minus direction.

Dr. C. V. Weller was good enough to prepare and examine sections of a large block of tissue removed from the infarcted area. He reported that the heart muscle in this region showed patchy necrobiotic alteration and areas of early fibroblastic proliferation. Leucocytic infiltrations were seen at the margins of the ischemic regions.

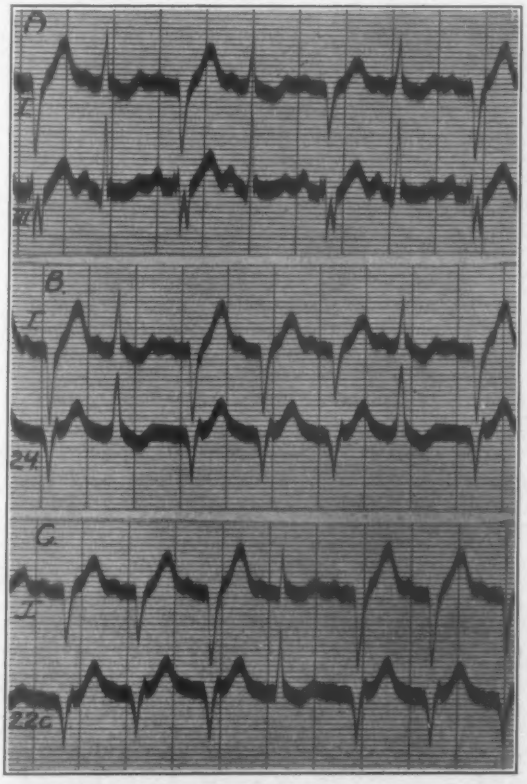

Fig. 3.—Experiment 1 (Dog 38). A.—Standard Leads I and III after attempt to cut the right branch of the His bundle. Partial right bundle branch block is present. B.—Standard Lead I (above) and a direct lead from point 24, taken with the ordinary soft-tipped electrode. C.—Standard Lead I (above) and a direct lead from the right ventricular cavity obtained by thrusting a sharp electrode through the ventricular wall at point 22. For the location of these points see Fig. 7.

Experiment 2 (Dog 42).—In this instance the electrocardiographic study was made two days after ligation of the right coronary artery. The standard electrocardiogram taken before the chest was opened is not obviously abnormal. Three precordial leads were also taken; one from a disk 5 cm. to the right of the midline; one from a disk in the midline 12.5 cm. from the episternal notch; and one from a disk 7.5 cm. to the left of the midline. The three disks were sewed beneath the skin and were arranged along a line extending from the right upper to the left

lower part of the precordium. These leads show no unequivocal signs of myocardial infarction, but in the first two the preintrinsic downward

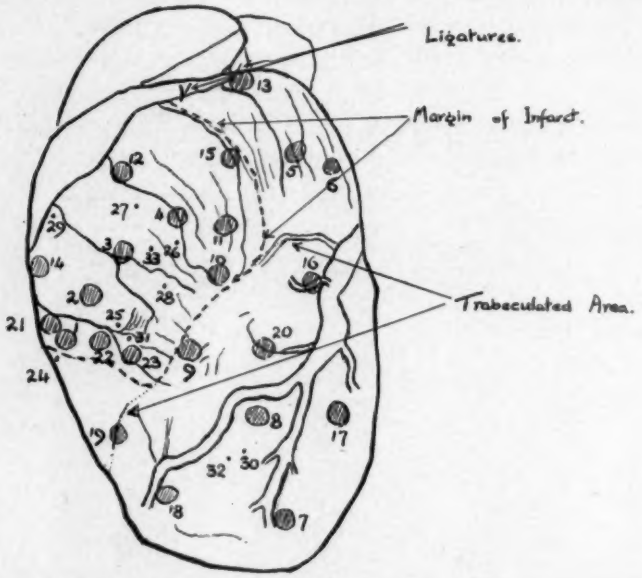

Fig. 4.—Experiment 2 (Dog 42). Outline drawing showing the location of the points from which direct leads were taken. The dotted line marks the approximate boundaries of the infarct.

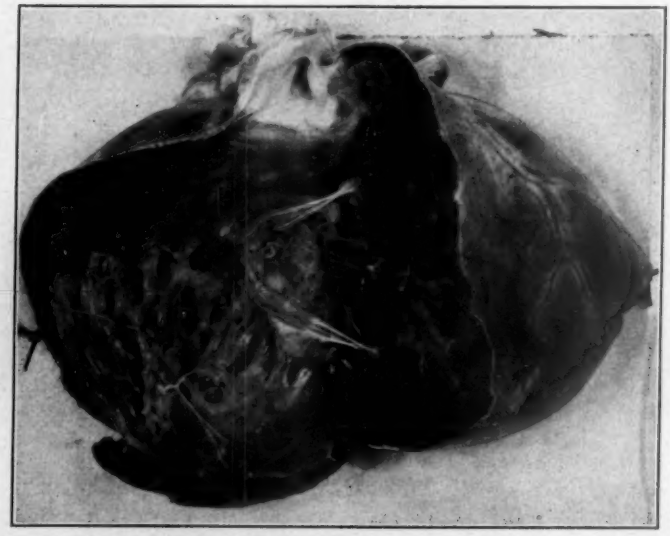

Fig. 5.—Experiment 2 (Dog 42). Photograph of the endocardial surface of the infarcted region.

deflection is unusually small. When the heart was exposed the infarct was clearly seen but its margins were not very sharply defined. An outline drawing of the heart which shows where the ligatures were placed

and the location of the infarcted area is shown in Fig. 4. The points explored by means of direct leads are indicated on this sketch. A photograph of the endocardial surface of the infarcted region is reproduced in Fig. 5. A large number of the curves obtained appear in Fig. 6.

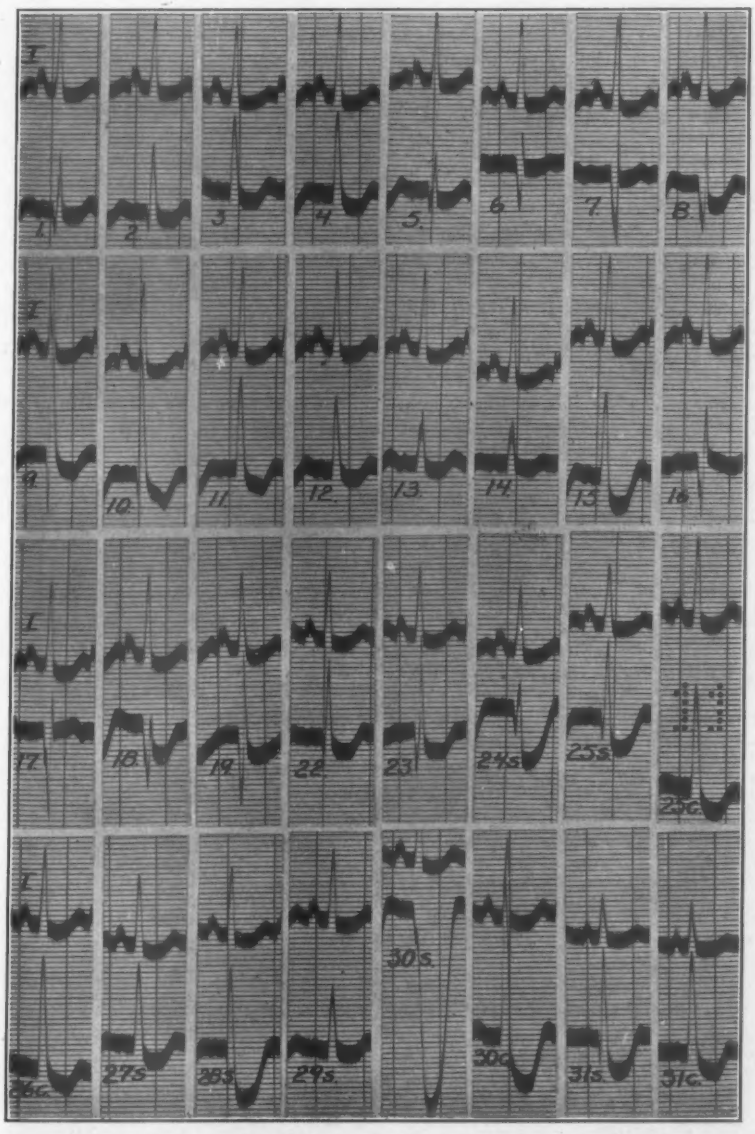

Fig. 6.—Direct leads from the points bearing corresponding numbers in Fig. 4. The upper curve of each record is standard Lead I. The letter *S* indicates that a sharp electrode was used and was pressed against the epicardial surface. The letter *C* indicates that the sharp electrode was thrust through the ventricular wall into the ventricular cavity. In the direct leads relative negativity of the exploring electrode is represented by an upward deflection and a deflection of 1 cm. represents a potential difference of 20 mv.

The direct leads from points 5, 6, 7, 8, 9, 16, 17, 18, 19, and 20, which were definitely outside the boundaries of the infarcted area, all show QRS complexes which begin with a deep initial downward deflection and display an intrinsic deflection of large amplitude. These complexes are of the kind usually obtained when the heart is normal. In the leads from points 8, 18, and 20 there is some downward displacement of the RS-T junction which we attribute to injury to the subepicardial muscle produced by pressing the exploring electrode too firmly against the heart. The curve from point 13, which is also outside the infarcted region, lacks both an initial downward deflection and a definite intrinsic deflection. In this instance we believe that the electrode must have been placed too high so that it rested upon the nonmuscular tissue of the auriculoventricular groove.

The leads from points 4, 11, 12, 14, and 15 yielded ventricular complexes consisting of a single large upright spike followed by a U-shaped T deflection. These complexes differ in no way from those which, in other experiments, occurred in leads from the surface of infarcts extending completely through the wall of the left ventricle.

The curves from points 3 and 21 are similar to those described in the preceding paragraph but show a trace of an initial downward movement preceding the large upward deflection. In the curves from points 1, 2, and 22 this initial downward deflection is larger and in the curves from points 10 and 23 it is still larger and not definitely subnormal in size.

We may now consider the curves obtained by using the sharp stab electrode. Leads from the right ventricular cavity were taken by thrusting this electrode through the ventricular wall at points 26, 27, and 31. These curves closely resemble those obtained from the epicardial surface at points 4, 11, 12 and 15 with the ordinary soft-tipped electrode. The deflections of the lead from the left ventricular cavity taken by forcing the stab electrode through the wall at point 30 are of similar outline but of much larger size. No trace of an initial downward or plus deflection is present in any of these curves. When the sharp electrode was pressed against the epicardial surface of the left ventricle at point 30, a monophasic ventricular complex was recorded. At points 27 and 29, which were on the infarcted region, the same procedure yielded curves no different from those obtained with a soft electrode at neighboring points. The absence of RS-T displacement in these leads indicates that at these two points the ventricular wall was dead. The two curves obtained with the sharp electrode from the epicardial surface at points 25 and 31 are almost identical. Unlike those from the ventricular cavity at the same points, they display a distinct initial downward deflection. They differ from the cavity curves also as regards the level of the RS-T junction and the depth of the U-shaped T deflection. The first of these differences must be ascribed to electrical forces generated by the outward spread of the excitatory process and hence to the presence of living

muscle in this part of the ventricular wall. The second difference must be attributed to injury sustained by this muscle when the sharp electrode was pressed against it. The curves obtained with the stab electrode at points 24 and 28 show still greater RS-T displacement, which indicates that in these regions also the ventricular wall contained living muscle.

After the leads described had been taken an attempt was made to cut the right branch of the bundle of His. Ventricular complexes characteristic of canine right branch block were recorded immediately afterward, although subsequent examination failed to reveal a cut definitely transecting the bundle branch. After bundle branch block had been produced a lead from the right ventricular cavity at point 33 and a surface lead from the same point (Fig. 7) yielded ventricular complexes identical in form, which began with a prominent initial downward deflection. Post-mortem examination revealed that in the neighborhood of points 1, 22, 23, 25, and 31 the infarction was distinctly patchy, whereas in the neighborhood of points 3, 4, and 27 the ventricular wall appeared to be uniformly involved. Microscopic examination of several blocks of

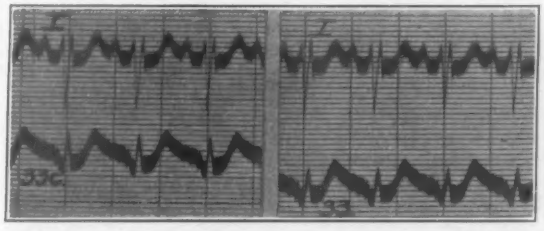

Fig. 7.—Experiment 2 (Dog 42). Curves taken after attempt to cut the right branch of the His bundle. Right bundle branch block is present. The upper curve in each record is standard Lead I. The lower curve on the left was obtained by thrusting the sharp electrode through the ventricular wall at point 33. The lower curve on the right was obtained from the epicardial surface at the same point with the ordinary soft-tipped electrode.

tissue removed from the infarcted region showed areas of simple necrosis and of necrobiosis with active leucocytic infiltration. Beneath the endocardium and around the blood vessels there was early calcification. In certain areas the process extended completely through the wall, although it appeared more marked on the endocardial side (Dr. Weller).

COMMENTS

The observations described demonstrate that direct leads from the outer surface of an infarct which involves the whole thickness of the right ventricular wall yield ventricular complexes of the same form as those seen in direct leads from the surface of an infarct which extends completely through the left ventricular wall. In the case of infarcts of the former as in the case of infarcts of the latter kind, leads from the epicardial surface and leads from the adjacent portion of the ventricular cavity yield curves that are practically identical when the ventricular wall contains no muscle capable of responding to the excitatory

process. This is true not only when the potential of the ventricular cavity is negative throughout the QRS interval, as is normally the case, but also when the potential variations of the ventricular cavity are altered by section of the bundle branch which supplies the infarcted ventricle. The effect of bundle branch block upon the potential variations of the homolateral and contralateral ventricular cavities has been discussed in a previous article. It should be emphasized that when the infarcted ventricle is activated later than its fellow, the QRS complex of direct and semidirect leads from the infarcted region begins with a plus deflection and not with a minus deflection. Infarction of the left ventricle cannot be expected to lead to disappearance of the preintrinsic plus deflection of the QRS complex of precordial leads if left bundle branch block is present.

In those experiments in which the right coronary artery was ligated, striking changes in the T deflection of direct leads from the margins of the infarcted region were not recorded, possibly because the electrocardiographic studies were not made at the proper time. The changes of this kind observed following ligation of the anterior descending branch of the left coronary artery were never found more than twenty-four hours after this operation. All of the right ventricular infarcts explored were at least forty-eight hours old.

Certain differences between the curves obtained from parts of right ventricular infarcts where some muscle was still capable of responding to the excitatory process and those obtained from parts of left ventricular infarcts which contained living muscle should be noted. In the case of the thick-walled left ventricle the infarct ordinarily involved a much larger area on the endocardial than on the epicardial surface. Direct leads from regions where only the inner layers of muscle were dead yielded curves of a distinctive type in which the QRS complex consisted of an abnormally large initial upward or minus deflection followed by a preintrinsic downward deflection and an intrinsic upstroke, both of subnormal voltage.[3] Curves of this kind were not obtained from the right ventricle. In the case of this relatively thin-walled chamber the boundaries of the epicardial aspect of the infarct were the same as the boundaries of its endocardial aspect in all the animals studied. In both of the experiments described an abnormally small preintrinsic downward or plus deflection occurred in direct leads from certain parts of the infarcted region. Since this deflection was not present in leads from the adjacent part of the ventricular cavity it obviously represented electrical forces produced by living muscle in the infarcted ventricular wall. The presence of this living muscle was also disclosed by the appearance of conspicuous RS-T displacement when a sharp electrode was substituted for the ordinary soft-tipped electrode. Theoretically, changes in the QRS complex of the kind in question might be produced either by infarction involving only the outer layers of the ventricular

wall, which would have the same effect as a reduction in the thickness of the muscle, or by a lesion affecting the inner and outer layers to the same extent without killing all of the fibers in either. A lesion of this kind would reduce the voltage developed during activation of the ventricular wall and hence the potential difference between the epicardial and the endocardial surfaces during the QRS interval. Since we could not demonstrate that the infarction was confined to the outer layers of muscle, the second of these two possible interpretations of the observations in question is probably the correct one.

SUMMARY

Infarction of the wall of the canine right ventricle was produced by ligation of the right coronary artery. This operation was carried out aseptically, and the chest wall was restored. After the lapse of a period sufficiently long to cause death of the fatally injured muscle the heart was exposed, and its anterior surface was explored by means of direct leads. A sharp electrode which could be thrust into or through the ventricular wall was used to obtain leads from the ventricular cavities and to determine whether the infarcted ventricular wall contained living muscle.

Direct leads from the outer surface of right ventricular infarcts which extended completely through the right ventricular wall yielded curves of the same kind as those obtained in earlier experiments by leading from the surface of left ventricular infarcts of the same kind. Both before and after section of the right branch of the bundle of His, leads from the surface of the infarct and leads from the neighboring part of the right ventricular cavity gave practically identical results.

In leads from regions where the infarcted right ventricular wall contained living muscle, the preintrinsic plus deflection of the QRS complex was present but abnormally small. In surface leads from regions where the wall contained no living muscle and in leads from the ventricular cavity this deflection was absent when the cardiac mechanism was normal. When right bundle branch block was induced, a prominent initial downward or plus deflection was present, both in cavity and in surface leads.

It has recently been recommended[9] that in taking direct leads of the kind used in this study the galvanometer connections be so made that relative positivity of the exploring electrode is represented by an upward deflection. In the curves reproduced in this article relative negativity of the exploring electrode is represented by an upward deflection.

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THE CARDIAC OUTPUT IN ARTERIAL HYPERTENSION*

PART II. A STUDY OF ARTERIAL HYPERTENSION PRODUCED BY CONSTRICTING THE RENAL ARTERIES IN UNANESTHETIZED AND ANESTHETIZED (PENTOBARBITAL) DOGS

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THERE have been relatively few studies[1-6] of cardiac output in arterial hypertension, and these have shown variable results. Disagreement has come in part from the use of different methods, but also from differences in manipulation by those who have used the same method. Lack of uniform criteria in the selection of subjects for study has been another source of error. The clinical classification of hypertension has changed rapidly and has not yet reached a point where diagnostic criteria have been clearly established and accepted. Undoubtedly the reported results have included patients of varying types and in different stages of various diseases.

Holman's study[7] of the cardiac output in hypertension, in which he used a single method and the same patients continuously over a period of several years, has not shown that any consistent abnormality characteristic of arterial hypertension exists. Like normal persons, some of the members of this group exhibited different levels of cardiac output. If hypertension is associated with changes in cardiac output, the difference seems to lie within the normal range. Study of individual cases should settle the question, but the opportunity is rarely given to observe the effect on cardiac output of the development or recession of elevated arterial pressure.

Since it is now possible to produce hypertension in dogs (Goldblatt, Lynch, Hanzal and Summerville[8]) and subsequently to relieve it, an experimental approach to the problem is open. Cardiac output methods and normal standards are, furthermore, fairly well understood for dogs. Knowledge is insufficient to decide whether hypertension produced by constricting the renal arteries is identical with any form of hypertension seen in human beings. Sufficient data exist to show some similarity between them.

METHODS

Adult, healthy dogs, with docile dispositions and weights ranging between 10 and 15 kg., were selected. Their cardiac output was measured by the technique based upon the Fick principle described by Marshall.[9] The oxygen consumption was measured with a clinical spirometer, on the tracing of which the respiratory rate was afterward counted. The animals were trained to lie relaxed and quiet on

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TABLE I

DATA ON CARDIAC OUTPUT

DOG	DATE	STATE	OXYGEN CONSUMPTION C.C./MIN.	ARTERIAL BLOOD VOL./%/OXYGEN	VENOUS BLOOD VOL. %	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT LITER/MIN.	INDEX LITER/MIN./SQ. M.	BLOOD PRESSURE	RESP. PER MIN.	PULSE RATE PER MIN.	HB. R.B.C.	REMARKS
No. 2	2/ 2/37	Nemb. deep*	80.7	18.84	15.64	32.0	2.5	3.9		4-5	150		
Male	2/24/37	Nemb. deep	82.8	16.67	13.14	35.3	2.3	3.7		3-4			
13.5 kg.	3/ 1/37	Unanest'd	97.5	19.14	13.98	51.6	1.9	3.1	140/90		80		
	3/ 8/37	Unanest'd	92.1	17.06	12.66	44.0	2.1	3.4	146/98		70		
	3/17/37	Nemb. light	99.8	17.80	13.11	46.9	2.1	3.3	144/90	5-8	105		Sick; anemic.
		Renal artery clamp applied—developed hypertension											
	6/ 2/37	Unanest'd	99.9	10.15	3.74	64.1	1.6	2.3	236/170	22	90	61% 4,904,000	
	6/ 4/37	Unanest'd	103.6	9.31	2.95	63.6	1.6	2.6	196/152		100?	4,064,000	Convulsions; died.
No. 4	2/17/37	Nemb. deep	87.2	13.44	9.44	40.0	2.2	3.9		7	130		
Female	5/21/37	Unanest'd	118.8	19.08	14.74	43.4	2.7	4.0	156/100	24			
15 kg.	5/24/37	Unanest'd	115.2	17.61	12.90	47.1	2.4	3.5	130/76	19			
	6/ 8/37	Unanest'd	100.6	19.22	15.10	41.2	2.4	3.4	132/84	16			
	6/10/37	Renal artery clamp applied—developed hypertension											
	6/14/37	Unanest'd	99.8	19.58	14.70	48.8	2.0	2.9	230/162	22			
	6/15/37	Unanest'd	100.3	19.36	15.15	42.1	2.4	3.4	220/156	21			
	6/17/37	Unanest'd	105.2	17.81	13.8	40.1	2.6	3.8	182/124	16			

*Pentobarbital.

TABLE I—CONT'D

No. 5 Male	5/24/37	Nemb. deep	90.5	15.29	12.38	29.1	3.1	4.8	136, 122	10	150		Van Leersum loop.
13.5 kg.	3/ 8/37	Nemb. light	77.3	15.10	11.03	40.7	1.9	3.0		24	95		
	3/15/37	Nemb. light	75.6	16.83	12.96	38.7	2.0	3.1	148	18	105		
	3/24/37	Renal artery clamp applied—developed hypertension											
									190				Unanest'd;
	3/29/37	Nemb. light	82.7	18.10	13.51	45.9	1.8	2.9	140	20	120		anest'd
No. 8	3/22/37	Nemb. light	69.8	12.79	18.36	44.3	1.6	2.5	150/86	18	90		
Female	4/ 5/37	Unanest'd	123.2	19.07	12.82	62.5	2.0	3.2	164/94	20	96		
14 kg.	4/14/37	Unanest'd	87.8	18.36	14.01	43.5	2.0	3.1	110/68				
	4/28/37	Unanest'd	107.2	17.83	11.75	60.8	1.8	2.6	150/80	28	85	74%	
	5/ 5/37	Unanest'd	91.6	19.14	13.95	51.9	1.8	2.6	138/80	24			
	5/ 8/37	Renal artery clamp applied—developed hypertension											
	5/12/37	Unanest'd	99.8	15.73	9.90	58.3	1.7	2.7	196/137	26		82%	
												5,848,000	
	5/19/37	Unanest'd	87.7	17.15	12.23	49.2	1.8	2.6	216/146	18		86%	
												7,104,000	
	6/11/37	Unanest'd	78.0	19.19	15.05	41.4	1.9	2.7	126/74	27			
No. 10	5/ 3/37	Anest'd	85.0	15.13	12.91	22.2	3.8	5.6	136/82	18			
Female	5/10/37	Unanest'd	97.5	15.89	12.04	38.5	2.5	3.6	136/82	22			
16 kg.	5/14/37	Unanest'd	111.5	16.83	13.25	35.8	3.1	4.2	134/89	22		73%	
	5/19/37	Renal artery clamp applied—developed hypertension											
	6/ 3/37	Unanest'd	114.5	19.26	15.19	40.7	2.8	3.8	213/150	18			
	6/ 9/37	Unanest'd	102.0	20.00	16.57	34.3	2.9	4.0	230/158	23			
	6/21/37	Second renal artery clamp applied—hypertension increased											
	6/23/37	Unanest'd	116.6	19.85	15.05	48.0	2.4	3.2	260/190				
	6/30/37	Unanest'd	115.0	21.91	17.45	44.6	2.6	3.5	230/160	20			
No. 11	4/30/37	Nemb. light	84.0	14.09	9.80	42.9	2.0	3.2	160/90	20	90		
Female	5/10/37	Unanest'd	102.1	16.08	10.34	57.4	1.8	2.8	168/104	22	84		
14.5 kg.	6/ 1/37	Unanest'd	110.7	16.50	10.89	56.1	2.0	2.9	164/108	20	80		
	6/ 3/37	Renal artery clamp applied—developed hypertension											
	6/ 7/37	Unanest'd	112.9	15.82	10.78	50.4	2.2	3.0	180/120	30			
	6/11/37	Second renal artery clamp applied—hypertension increased											
	6/14/37	Unanest'd	94.3	12.69	8.00	46.9	2.0	3.0	208/140	26			
	6/16/37	Unanest'd	102.5	12.35	8.02	43.3	2.3	3.4	200/138				
	6/30/37	Unanest'd	99.8	16.35	10.26	60.9	1.6	2.6	188/130	20			

their left sides. An airtight connection between the apparatus and the dogs' muzzles was made by the Blalock mask,[10] the efficiency of which was readily tested by increasing the pressure within the circuit once or twice during the test period. With the chest wall carefully anesthetized by novocain and with the animal turned gently upon its back, samples of mixed venous blood and arterial blood were taken by direct puncture from the right and left ventricles, in the order named. Occasional arterial samples were drawn from a femoral artery. The dogs were not disturbed by the procedure unless a rib was struck or the pericardium was scraped or pulled.

Samples of blood were collected under mercury in oxalated ice-cold glass tonometers. Their oxygen content was analyzed in duplicate, within one hour, by the Sendroy modification[11] of the Van Slyke[12] method. They were kept on ice in the interval.

The surface area used in calculating the cardiac output index was estimated by the Meeh-Rubner formula,[13] which is believed to be sufficiently accurate because the dogs used were similar to each other in size and state of nutrition.

Systolic and diastolic blood pressures were taken by auscultation with a small bell over the dorsalis pedis artery while the dogs lay quietly on their sides. In one dog (No. 5) a van Leersum carotid loop had been prepared. Numerous blood pressure readings were made, but only one representative set of figures was recorded for each test. The pulse rate counts were similarly condensed.

The dogs fasted from four o'clock of an afternoon until the experiments were performed about twenty-four hours later. They rested on the table for at least fifteen minutes. Measurements of the cardiac output of each animal were made at intervals until satisfactory uniform values were established to serve as controls. The operation for bringing on arterial hypertension was then undertaken, and, as soon as the animal recovered and hypertension became established, the observations were repeated. A well-trained dog behaved as well after operation as before. In one instance (dog No. 8) observations were continued after spontaneous return of the blood pressure to normal. In order to maintain body weight and normal hemoglobin in the red blood cells the dogs were given generous diets, including raw meat and, sometimes, iron. The red cells were counted in the standard chamber, and hemoglobin was estimated with the Sahli hemoglobinometer. Slight degrees of postoperative anemia disappeared promptly except in dog No. 2, which grew steadily more ill and finally died in a state of clonic convulsions, the blood urea nitrogen being 136 mg. per cent.

Some observations were made on cardiac output under the influence of general anesthesia. Pentobarbital (nembutal) was given intravenously in doses of 15 to 35 mg. per kilogram of body weight. The size of the dose depended upon the depth of anesthesia that was desired. Doses close to the minimum or maximum amounts were usually injected, and the states of anesthesia were described as either "light" or "deep."

RESULTS

Six dogs were studied before and after arterial hypertension was established (Table I). Of these, one (No. 5) was observed solely under the influence of general anesthesia, and the results in another (No. 2) were invalidated by the poor condition of the animal after operation. The effect of arterial hypertension upon the cardiac output was judged, therefore, from the results with four dogs, Nos. 4, 8, 10, and 11 (Fig. 1). Well-marked arterial hypertension developed in all instances, but the pressure was higher in some than in others. Since there was no apparent

change in cardiac output during even the most marked hypertension (No. 10), there was no occasion for attempting a correlation with any particular blood pressure level. As in human beings, the variations in

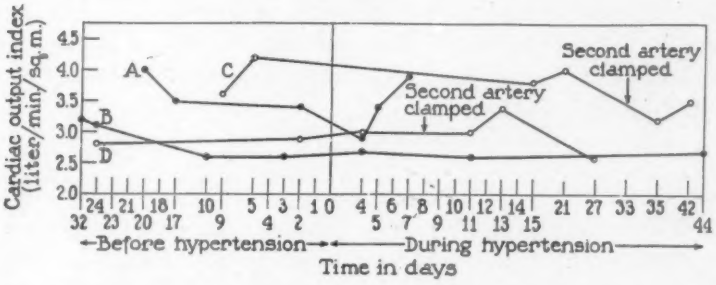

Fig. 1.—The cardiac output expressed as the cardiac index of four unanesthetized dogs is plotted before and during arterial hypertension induced by constriction of the renal arteries. The ordinates show the cardiac index; the abscissas, time in days. Zero abscissa is the time of the first operative procedure. Subsequent operations are shown by arrows. Reading to left and right of zero are observations during normal and hypertensive states, respectively. Line A represents dog No. 4; line B, dog No. 8; line C, dog No. 10; and line D, dog No. 11 (See Table I). The index of each animal is fairly constant; repeated measurements tend to be closer to each other (i.e., their own average) than to the average of a group. The output values for the group and for any individual are not different during hypertension from what they were before it was produced.

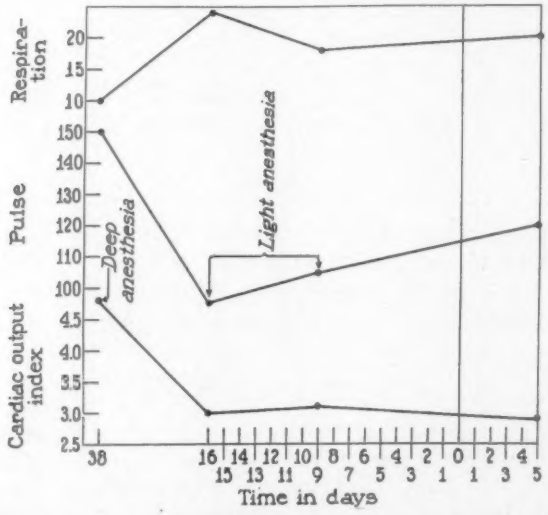

Fig. 2.—The cardiac output expressed as the cardiac index of a single dog (No. 5) is plotted under general anesthesia (pentobarbital), before and after establishing arterial hypertension by means of constriction of the renal arteries. Ordinates and abscissas are as in Fig. 1. In a test under deep anesthesia the cardiac output was greater, the pulse rate was faster, and the respiratory rate was slower than in two subsequent observations under light anesthesia. There was essentially no change in these functions after operation under light anesthesia.

each animal from an accustomed level tended to be smaller than the combined range encountered within a group (Fig. 1).

In dog No. 5, while the animal was under the influence of light pentobarbital anesthesia the cardiac output was the same after the renal artery

was constricted as before (Fig. 2). With this degree of anesthesia the cardiac output was approximately the same as with no anesthesia. Dogs No. 2 and 8 (Table I) exhibited this same phenomenon. The pulse, respiration, and metabolism were essentially undisturbed during light anesthesia (as compared with the values recorded without anesthesia), whereas in deep anesthesia the pulse rate increased, the respiratory rate decreased (Fig. 2), and the metabolic rate was depressed (dogs No. 2 and 4, Table I).

DISCUSSION

The results observed before operation were similar to Marshall's[9] observations on normal unanesthetized dogs. The outputs tended to be higher than 2.2 ± 0.3 liters per minute per square meter body surface, regarded as standard in normal human beings, but the number of observations made in dogs was insufficient to establish comparable figures. To ascertain the normal range lay outside this investigation. Since Starr and Collins[14] have shown that the rate at which blood flows is faster in dogs, the cardiac output may likewise differ. In this study it was necessary only to ascertain how closely repeated measurements agreed. Studies of the animals selected showed that when properly trained and accustomed to the procedure, the output varied less from day to day in individual animals than in the group, and less also when the output was at a low normal level. The fact that the cardiac output is high and that there is greater variation when it is suggests that this phenomenon is related to the dog's temperament and reaction to handling.

Pressure within the arterial system is, as is well known, the resultant, chiefly, of two opposing forces, cardiac output and peripheral resistance. The volume and viscosity of the circulating blood are also factors, but they may be neglected because they have been shown to remain normal in patients with arterial hypertension,[15, 16] and also in dogs with experimental hypertension.[17]

Inasmuch as these studies show that the cardiac output persists unchanged, the high blood pressure could have arisen only through the mechanism of increased peripheral resistance. The same conclusion was reached by Pickering,[18] and by Prinzmetal and Wilson,[19] who found the blood flow in the limbs of patients to be normal. They decided that resistance was increased by means of widespread hypertonus of the arterioles. Their interpretation is supported by the results of these experiments; a normal cardiac output would of course be impossible unless an adequate volume of blood were returned to the heart. It is conceivable that in a late stage of the disease changes in the vessel walls may narrow the vascular bed and result in decrease of the volume of peripheral blood flow, which would in turn diminish the cardiac output. Since the stage studied in these dogs was very early, and since the

outputs were no higher than normal, it seems unlikely that increased output is to be found involved in the mechanism in any stage in the course of arterial hypertension.

To avoid training the dogs, the use of pentobarbital was attempted but was abandoned very soon for two reasons: (1) Under its influence hypertension tended to disappear, and (2) observations of the cardiac output showed unexpectedly large variations. It is known that barbiturate anesthesia tends to lower the human blood pressure, especially in some patients with arterial hypertension. Similarly in these dogs hypertension was undoubtedly interrupted by release of peripheral resistance.

The amount of cardiac output in nonhypertensive dogs under the influence of pentobarbital seems directly proportional to the depth of anesthesia. When it is very light there is no depression of respiration, no tachycardia, no cyanosis, and the cardiac output is equivalent to that found in nonanesthetized animals. There is, in short, no essential disturbance of the circulation. In deeper degrees of anesthesia the respiratory rate fell by at least a half, the total oxygen consumption was reduced, the pulse rate rose, and the cardiac output increased. Since marked cyanosis was present, the fall in the rate of respiration was undoubtedly a result of direct action of the drug upon the respiratory center. Amytal has been reported to depress metabolism[20] and pentobarbital conceivably does so also, since they have similar pharmacologic properties. The increased cardiac output was accompanied by a decrease in the arteriovenous oxygen difference and marked tachycardia. Anoxemia without anesthesia has been shown to produce a similar effect in man[21] and may be credited with a primary etiological role in these dogs.

SUMMARY

1. The cardiac output of healthy unanesthetized dogs under standard conditions varies little from day to day.

2. In several dogs in which the normal range of cardiac output was known, acute arterial hypertension was brought on by constriction of the renal arteries. The cardiac output remained unchanged.

3. Since cardiac output remains unchanged, arterial hypertension seems to depend on peripheral vasohypertonus.

4. A light degree of pentobarbital anesthesia did not change the cardiac output of normal or hypertensive dogs. Anesthesia sufficiently deep to depress metabolism and respiration increased the pulse rate and cardiac output.

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HUMAN AUTONOMIC PHARMACOLOGY*

XVIII. Effects of the Intra-Arterial Injection of Acetylcholine, Acetyl-Beta-Methylcholine Chloride, Epinephrine, and Benzedrine Sulfate

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THE bodily response of man to drugs administered intra-arterially has been investigated by only a few workers. Ellis and Weiss[1] studied the effects of acetylcholine following its administration into the brachial artery, and Battro and Lanari[2] and Allen and Crisler[3] observed the effects of mecholyl and other vasodilator drugs following their intra-arterial administration in normal subjects and in patients with peripheral vascular disease.

This communication reports the effects of the intra-arterial administration of epinephrine, acetyl-beta-methylcholine chloride (mecholyl), acetylcholine and benzedrine sulfate (benzyl methyl carbinamine). If these drugs are given in amounts sufficient to produce a reaction in the tissues supplied by an artery and yet insufficient to reach the general circulation, certain phenomena appear which, because of their localization, can be more directly studied than when these drugs are given intravenously or intramuscularly with the production of general effects. For example, the sweating produced by acetylcholine and mecholyl limits itself to an extremity, and an artificial Raynaud-like reaction brought about by epinephrine can be experimentally produced and more intimately investigated.

MATERIAL AND METHODS

The subjects of this study were for the most part patients suffering from dementia precox. These patients have been the subjects of previous reports[4, 5, 6] from this laboratory and have been repeatedly shown by our present tests to be physiologically normal. The brachial artery was selected because of its accessibility. It was readily punctured by an ordinary 19 to 20 gauge needle over the point of maximal pulsation in the antecubital fossa.

Intra-arterial Administration of Acetylcholine.—Doses of acetylcholine varying from 0.01 mg. to 10 mg., in 0.1 c.c. of water, were injected into the brachial arteries of twelve subjects. Within thirty to sixty seconds following the injection goose flesh appeared on the injected arm, then mild to marked flushing, followed immediately by a variable degree of sweating over the hand and arm, extending to an area slightly above the

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antecubital fossa. The flushing was usually so distinct that the distribution of the brachial arterial tree was sharply outlined. Associated with the above reaction there was increased warmth of the hand and arm. The reaction reached its height in a few minutes and gradually subsided, disappearing in from three to ten minutes, depending on the dose and sensitivity of the patient. In none of the cases in which the smaller doses were used was there any flushing and sweating except in the injected extremity. When the larger doses were used the systemic blood pressure rose slightly, usually no more than 15 mm. Hg. In one case the blood pressure rose 30 mm. Hg, and in another case there was a slight fall in blood pressure. Following the injection of the smaller doses there was no change in systemic blood pressure. With doses ranging from 3 to 10 mg. a moderate rise in blood pressure occurred in the injected arm. With the minimal doses, flushing alone or flushing associated with mild sweating in the injected arm occurred.

Intra-Arterial Administration of Mecholyl.—(1) Mecholyl in doses of 0.1 mg. to 3 mg. in 0.1 c.c. of water was injected into the brachial arteries of nine subjects. Reactions similar to but correspondingly more marked than those obtained by acetylcholine occurred. A local reaction extending from slightly above the antecubital fossa to the end of the fingers occurred almost immediately following the injection, gradually subsiding in from five to ten minutes. Following the administration of the larger doses (3 mg.), the vasodilatation was extremely marked, and the veins stood out prominently. The diastolic pressure in the injected arm could not be measured because the sounds were still audible, even when the pressure in the cuff reached zero. There was only a slight fall in systolic pressure in either arm. In three cases in which extreme vasodilatation and sweating occurred, a pistol shot sound and a systolic and diastolic murmur were heard over the injected brachial artery (Duroziez's sign), due obviously to the greatly increased rate of blood flow toward the periphery associated with the marked vasodilatation.[7] Although in many instances the dose used was great enough to have caused marked general reactions if it had been given by vein, little, if any, general reaction occurred when the intra-arterial route was used.

(2) In eight cases it was found that the minimal reacting dose was between 0.001 mg. and 0.0001 mg. in 0.1 c.c. of water. With these doses either mild flushing or flushing combined with mild sweating of the hand occurred.

Combined Administration of Mecholyl and Atropine.—In five cases the intrabrachial injection of 0.5 mg. of mecholyl was preceded by the subcutaneous injection of atropine (1.3 mg), the mecholyl being given at the height of the atropine response. In no case were any observable local or general effects of mecholyl noted, showing that the local effects of this drug are inhibited by atropine, just as are all the systemic effects.

Combined Administration of Prostigmin and Mecholyl.—In three cases prostigmin (0.5 mg. intramuscularly) was given ten to 15 minutes

prior to the intrabrachial injection of 0.5 mg. of mecholyl. In two other cases both drugs were given simultaneously in the same dosage by the intrabrachial route. In the latter two cases, and in one of the others, the local reaction was very marked. In these cases a pistol shot sound and a systolic and diastolic murmur developed over the brachial artery, and within one to two minutes after the injection of the drugs sounds could be heard down to zero for several minutes. This reaction had been previously observed with mecholyl in doses not less than 3 mg. Thus, prostigmin definitely enhanced the mecholyl effect, acting in its well-established role as synergist[8] to this drug.

Only a slight change in systolic pressure occurred in the injected arm. The systemic blood pressure remained practically unaffected. Very slight, if any, general flushing or sweating occurred in any of these cases.

Intra-arterial Administration of Epinephrine.—(1) Twenty-four subjects were given epinephrine by the intrabrachial route in doses varying from 0.1 mg. to 0.3 mg. (0.1 c.c. to 0.3 c.c. of a 1:1,000 solution). Within a minute goose flesh appeared over the arm, and this was quickly followed by marked pallor beginning in the fingers and extending to the hand and arm up to the elbow; this was especially marked with the larger amounts, so that the arm and hand appeared blanched. With the increase in pallor the radial pulse became increasingly smaller in volume, so that in many cases it could not be felt, whereas the other radial pulse remained unchanged. Associated with the pallor there was marked coldness of the hand. The local reaction reached its height in a few minutes and gradually receded, usually lasting from ten to twenty minutes, in a few cases somewhat longer. In doses up to 0.1 c.c. of a 1:1,000 solution no effect on the systemic blood pressure or pulse was evident. In doses larger than 0.1 c.c. of a 1:1,000 solution slight elevation in general systemic blood pressure occurred. One subject, a neurotic, described the subjective sensations as follows: Within two minutes following the injection of 0.1 c.c. of a 1:1,000 solution of adrenalin the hand felt numb and the fingers were difficult to extend; there was a stabbing pain in the middle of the palm; the tips of the fingers were painful and the hand felt limp; after three minutes tingling of the finger tips began. These sensations continued for ten more minutes. Thirty minutes after the injection, the hand was still slightly pale.

(2) Since the above doses of epinephrine are far beyond the amount liberated in the limb under physiologic conditions, the same twenty-four subjects were given injections of increasing dilution into the brachial artery until minimal, but still definite, local reactions were obtained. It was found that 0.1 c.c. of a 1:100,000 to 0.1 c.c. of a 1:1,000,000 solution of epinephrine (0.001 to 0.0001 mg.) caused definite pallor of the hand, in some cases accompanied by diminution in volume and force of the

radial pulse. In two instances it seemed that the pallor was preceded by slight vasodilatation of the hand and forearm, but when the experiments on these two subjects were repeated, the initial vasodilatation could not be obtained. In most cases mild pilomotor response preceded and accompanied the pallor of the forearm. Following the suggestion of Fatherree and Allen[9] that vasodilatation must first be produced to study the extremes of sensitivity to epinephrine, the arm and hand of one patient were submerged in hot water until maximal vasodilatation occurred. The intra-arterial injection of 0.1 c.c. of a 1:1,000,000 solution of epinephrine then produced clear-cut, easily observable vasoconstriction of the forearm, hand, and wrist. In this same patient the same amount of epinephrine injected in the other hand, not previously vasodilated, produced no discernible effect.

Difference Between Intra-Arterial Administration of Benzedrine Sulfate and Epinephrine.—The injection of various doses of benzedrine sulfate into the arteries of several subjects produced no demonstrable local effects. The systemic effects, however, were marked and occurred exactly as if the drug had been injected into a vein or subcutaneously. In other words, benzedrine sulfate does not remain localized in the distribution of the artery but passes into the general circulation, so that obviously the drug is not destroyed or fixed in the tissues, such as is the case with epinephrine.

Intra-Arterial Administration of Epinephrine Followed by Mecholyl.—In four cases, 0.1 c.c. to 0.3 c.c. of a 1:1,000 solution of epinephrine (0.1 mg. to 0.3 mg.) was injected into the brachial artery, and at the height of the pallor 3 mg. of mecholyl were injected into the same vessel. Immediately following the latter injection small areas of vasodilatation occurred either over the back of the hand and arm or over the bend of the elbow. This vasodilatation disappeared quickly, to be replaced by the pallor due to the epinephrine. In no case was the mecholyl in the amounts given able to overcome the local response in the fingers. Slight, if any, general systemic reaction occurred in any of these cases.

In two cases prostigmin (0.5 mg. intramuscularly) was administered twenty minutes prior to the injection of 0.1 c.c. of a 1:1,000 solution of epinephrine, which was then immediately followed by an intra-arterial injection of 3 mg. of mecholyl. In one of these cases the epinephrine reaction was replaced by vasodilatation down to the metacarpophalangeal junction with no effect on the fingers, so that there was a sharp demarcation between the redness of the palm and the pallor of the fingers. The vasodilatation gradually spread to the fingers, so that eight minutes following the injection of the mecholyl the fingers became red, leaving that hand much warmer than the opposite hand. There was also a moderate general reaction as shown by a fall in systemic blood pressure, an increase in pulse rate, salivation, tearing, coughing, and sweating of the face and chest. In the other case, although the same doses of the drugs

were used, the marked pallor of the fingers was unaffected by the mecholyl, although moderate vasodilatation of the arm occurred. In two other cases the local responses produced by 0.1 c.c. of a 1:1,000,000 solution of epinephrine were not affected by 3 mg. of mecholyl when both drugs were given simultaneously into the brachial artery.

Intra-Arterial Administration of Mecholyl Followed by Epinephrine.—In five subjects mecholyl was injected into the brachial artery and followed, within one to three minutes, by adrenalin administered into the same vessel. Two of the subjects were given 0.1 mg. of each drug. Although a moderate local response to the mecholyl developed, the epinephrine overcame such a local reaction within one to three minutes, and the final effect was apparently in no way different from that which developed when the latter drug was given alone. In both cases, however, there was a rise in systemic blood pressure of 14 and 28 mm. Hg, respectively. In the other three cases a similar procedure was carried out, using 3 mg. of mecholyl and 0.1 mg. of adrenalin. In one case a moderate local mecholyl reaction was replaced in three minutes by pallor of the same parts. In the other two cases, however, the epinephrine response was definitely delayed, so that pallor occurred in eleven and thirty-three minutes, respectively, following the epinephrine injection. The blood pressure was not followed in the latter three cases.

DISCUSSION

The foregoing experiments indicate that acetylcholine and mecholyl, when given intravenously in dosage sufficient to cause definite general reactions, produce only a local response of the hand and arm on the injected side when administered intra-arterially. Within such dosage the usual absence of a general response indicates that these drugs are destroyed or fixed in the local tissues. Thus, 1 mg. of acetylcholine and 0.1 mg. of mecholyl produce marked vasodilatation of the vessels of the hand and arm without general reaction when injected into the brachial artery. This indicates that both these drugs act peripherally on the muscle cells of the blood vessels and the secretory cells of the sweat glands.

Epinephrine, injected intra-arterially in amounts from 0.1 mg. to 0.001 mg., causes a definite local response, as evidenced by pallor and coldness of the arm and hand, particularly of the fingers, without any systemic response. With the larger doses the pulse becomes smaller in volume and may disappear entirely. In the same subjects amounts as small as 0.0001 mg. produce a local constrictor response. Once a local reaction is established by the smallest effective dose of epinephrine, mecholyl in amounts up to 3 mg. will only partly counteract the epinephrine reaction. These data indicate that the amount of epinephrine sufficient to produce the vasoconstrictive phenomenon of

Raynaud's disease in the extremities must be about 0.001 mg. to 0.0001 mg. Furthermore, since 3 mg. of mecholyl intra-arterially will not replace, or only incompletely replace, the local epinephrine reaction, it would a priori appear doubtful that parasympathomimetic drugs, whether given intra-arterially or by iontophoresis, would be efficacious in the treatment of Raynaud's disease. Doses larger than 3 mg. of mecholyl might counteract the epinephrine reaction but would be likely to produce undesirable or untoward general effects.

Because of the absence or very mild evidence of general reactions, it appears that relatively large amounts of epinephrine are fixed or destroyed in situ when administered intra-arterially. When injected into a vein and distributed throughout the body, there is a general reaction, probably because cells throughout the body are affected.

When mecholyl is given prior to the epinephrine, there may be sufficient local dilatation of the peripheral vessels to allow the latter drug to reach the general circulation. Again, the fact that epinephrine may still cause a local response several minutes after its intra-arterial injection if it has been preceded by large intra-arterial doses of mecholyl indicates that it becomes fixed in the tissues for a relatively long period of time.

SUMMARY AND CONCLUSIONS

Acetylcholine, mecholyl, epinephrine, and benzedrine sulfate in varying amounts were introduced into the brachial artery of man. In some instances combinations of atropine and mecholyl and, in others, prostigmin and mecholyl were similarly injected.

(1) Intra-arterial injections of acetylcholine in amounts varying from a minimal dose of 0.01 mg. to 10 mg. produced a local reaction of the arm and hand, consisting of vasodilatation, pilomotor stimulation, and usually sweating, without any general reaction except a slight rise in general blood pressure following the larger doses.

(2) Intra-arterial injections of mecholyl in amounts varying from 0.0001 mg. to 3 mg. effected similar, although correspondingly more marked, local reactions than acetylcholine, in the larger doses producing a marked change in the local blood pressure. In some cases pistol shot sounds and Duroziez's phenomenon appeared and it became impossible to measure the diastolic pressure. General reactions appeared only in those cases in which more than 2 mg. were used or when the effect was enhanced by prostigmin. Atropine was able to prevent completely the mecholyl reaction.

(3) The minimal intra-arterial effective dose was found to be (a) in the case of acetylcholine 0.01 mg. to 0.1 mg., and (b) in the case of mecholyl 0.0001 mg. to 0.001 mg. Slight or no general reaction occurred following the intra-arterial injection of less than 10 mg. of acetylcholine and less than 2 mg. of mecholyl.

(4) Intra-arterial injections of epinephrine in widely varying doses (0.0001 mg. to 0.3 mg.) produced vasoconstriction of the arm and hand as shown by pallor and coldness in the areas supplied by the brachial arterial tree, a reaction similar in many respects to that seen clinically in Raynaud's disease.

(5) The minimal effective intra-arterial dose of epinephrine was found to be between 0.0001 mg. to 0.001 mg. The tissues of the hand are able to break down comparatively large amounts of epinephrine, as evidenced by the lack of general reaction to a dose below 0.1 mg.

(6) The vasoconstriction produced by epinephrine even in minimal amounts was not completely overcome by doses of mecholyl as large as 3 mg. On the other hand, the prior intra-arterial administration of mecholyl may not only produce sufficient local vasodilatation to allow the subsequently administered epinephrine to reach the general circulation, but also may delay the local response of the latter drug, a phenomenon which suggests that epinephrine under such conditions remains in the local tissues and is potentially active for a relatively long period of time.

(7) Benzedrine sulfate when injected intra-arterially produces general effects but not especially marked local effects. In other words, this drug is not easily destroyed by the tissues and consequently may circulate for a considerable period of time. It is noteworthy that acetylcholine, mecholyl, and epinephrine cannot be administered by mouth with any degree of success, whereas benzedrine sulfate is effective when so administered. It is probable that the potentiality of a drug for oral administration may be tested by observing its effects when injected intra-arterially.

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THE CLINICAL SIGNIFICANCE OF A PERSISTENT DEPRESSION OF THE RS-T SEGMENT IN THE ELECTROCARDIOGRAM

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I. INTRODUCTION

IN THE last ten years, since the electrocardiogram ceased to be a method of analyzing disorders of the cardiac rhythm only and became an important aid in the diagnosis of other diseases of the heart, much stress has been laid on deviation of the RS-T segment from the isoelectric line. These deviations in acute coronary occlusion, as described by Pardee[1] and analyzed and classified by Parkinson and Bedford[2] and Barnes and Whitten,[3] are well known. Similar changes have been described in transient myocardial ischemia. Depression of the RS-T segment with or without inversion of the T-wave has been seen both in attacks of spontaneous angina pectoris and that provoked by exercise (Feil and Siegel,[4] Parkinson and Bedford,[5] Brow and Holman,[6] Goldhammer and Scherf,[7] Hausner and Scherf[8]). It has been shown that general anoxemia induced by breathing of an oxygen-poor mixture causes a depression of the RS-T segment not only in patients with an insufficient coronary circulation, but also in normal subjects (Rothschild and Kissin,[9] Katz and Hamburger[10]). Büchner[11] found similar changes in the electrocardiogram of rabbits after an acute massive hemorrhage and demonstrated small areas of necrosis in the heart muscle of these animals. Electrocardiographic changes of this type were found in man in anemia,[12] hypoglycemia,[13] carbon monoxide poisoning and in other conditions, the common feature being a state of malnutrition of the heart muscle. Among other causes of RS-T deviation are certain drugs, especially digitalis,[14] infections[15] (acute rheumatism, diphtheria), pericarditis,[16] and pulmonary embolism.[17]

There are, however, cases in which the deviation of the RS-T segment is permanent and progressive. Pardee[18] described this abnormality of the electrocardiogram and considers that the cause of it is unknown. He suggests that the contraction process may develop potential sooner after QRS because of the greater activity of the hypertrophied muscle. On the other hand, Weber and his associates[19] accept a depression of the RS-T segment with or without an inverted T-wave as the most characteristic sign of an inadequate blood supply

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to the heart muscle, which they call "coronary insufficiency." Their theory, based on the above cited experiments of Büchner, has found its way into most textbooks of electrocardiography written in the German language,[20] although it has been criticized lately by Schellong and his associates.[21]

In the routine electrocardiographic work in this department I noticed that a persistent depression of the RS-T segment is not an uncommon finding, and these investigations were carried out in order to see whether this abnormality is related to any special type of heart disease or syndrome.

II. METHODS OF INVESTIGATION

The investigations were carried out in the following way:

1. Electrocardiograms of 150 normal subjects between the ages of 15 and 40 years were used as controls.

2. Two thousand electrocardiographic curves taken in the routine work of the department in 1936 and 1937 were examined in order to discover the incidence of a permanent depression of the RS-T segment.

3. All cases of heart disease in which this abnormality occurred were analyzed, especially in regard to the relationship of the electrocardiogram to the clinical course of the disease.

The tracings were made either with the standard Cambridge string galvanometer or the Victor electrocardiograph. In about 40 per cent of the cases, in addition to standard leads, precordial leads were taken. The technique of the chest leads is described elsewhere[22]; the exploring electrode was placed at the apical, left pectoral, and right pectoral regions, and the indifferent electrode on the right arm or left leg.[23]

A permanent depression of the RS-T segment was diagnosed when two or more tracings taken within a month or more showed this change. In a few cases in which only one record was available, every possible factor influencing the electrocardiographic curve was considered before the cases were included in the series.

In measuring depression or elevation of the RS-T segment, care was taken to exclude apparent deviation due to exaggerated auricular T-waves,[24] to a prominent U-wave, or to respiratory effects upon the level of the base line. Technical faults, especially overshooting, were given due consideration. No cases of bundle branch block were included. Because of some difficulties in ascertaining the level of the RS-T segment, a few rules were followed: (1) The depression or elevation of the RS-T segment was measured from the base of the preceding P-R segment if the latter was horizontal. (2) When the P-R segment showed no distinct level, the RS-T segment was compared with the following T-P segment whenever possible. (3) Records in which the heart rate was over 110 were excluded because the RS-T segment was so shortened as to make it almost impossible to gauge its level.

From the clinical point of view particular stress was laid on presence or absence of angina pectoris, on the size of the heart as estimated radiologically, and on the presence or absence of heart failure.

III. RESULTS

A. NORMAL CONTROLS

The electrocardiograms of 150 healthy young people between 15 and 40 years of age were examined. It was found that both in the standard and in the chest leads the RS-T segment was almost invariably

isoelectric. In a very small proportion of cases there was a slight deviation of the segment above or below the isoelectric line in the standard leads, the maximum being 0.25 mm. In chest leads the deviation was more common but did not exceed 1 mm. It seems safe to conclude that the upper limit of normal variations is 0.5 mm. (0.05 mv.) in standard leads and 1.5 mm. (0.15 mv.) in chest leads.

B. ROUTINE ELECTROCARDIOGRAMS

Two thousand curves were examined, and 178 were found in which a persistent depression of the RS-T segment was present. In 56 of these the depression was due to digitalis, and these records were excluded from further study.

In the remaining 122 cases the following diseases were found:
Hypertensive heart disease in 69 cases,
Syphilitic aortic valvular disease in 19 cases,
Nonsyphilitis aortic valvular disease in 8 cases,
Coronary artery disease in 7 cases,
Rheumatic mitral valvular disease in 9 cases,
Cor pulmonale in 4 cases,
Congenital heart disease in 1 case,
Infective endocarditis in 1 case,
Myxedema in 2 cases,
Thyrotoxicosis in 2 cases.

These figures reveal that a depression of the RS-T segment may occur in all types of heart disease, the distribution of cases corresponding roughly to the frequency of the disease in the material examined.

Examination of the curves showed that permanent deviation of the RS-T segment may occur as a depression or as an elevation, but that the former was the more constant and the more striking. When elevation of the RS-T segment does occur, it is invariably as a reciprocal effect of the depressed RS-T segment in the opposed lead. It was found in 28 per cent of the present series and occurred only in association with left or right axis deviation. Thus in left axis deviation, when the RS-T segment is depressed in Lead I, it may be elevated in Lead III, the amplitude of the depression being usually greater than that of the elevation. The deviation always occurs in the opposite direction to that of the main ventricular complex. Elevation was never present in more than one lead and was never found in Lead II. It was not found in the absence of a more striking depression in the opposed lead.

Two types of RS-T depression can be distinguished: the common type shows a depression of the RS-T take-off, and the curve runs horizontally under the isopotential level into an upright, diphasic or inverted T. In other cases the RS-T depression simulates that pro-

duced by digitalis, in which the RS-T take-off is isoelectric or slightly depressed and the RS-T segment moves downwards in a straight line to an inverted or diphasic T-wave. This "sagging" RS-T depression occurred in 13 cases (11 per cent) in which digitalis treatment was excluded.

RS-T depression of the common type measured from 0.5 to 2 mm. in amplitude. It was found in one or two leads, but never in all three leads. It occurred particularly in cases of axis deviation in the lead in which the maximum QRS deflection was upwards, i.e., in Lead I in left axis deviation and in Lead III in right axis deviation. The facts are presented in Table I.

TABLE I

RELATIONSHIP OF DEPRESSION OF THE RS-T SEGMENT TO NORMAL OR ABNORMAL T-WAVES

TYPE OF ELECTROCARDIOGRAM	RS-T SEGMENT DEPRESSED IN ONE LEAD	RS-T SEGMENT DEPRESSED IN TWO LEADS	RS-T DEPRESSION AND ELEVATION IN THE OPPOSED LEAD
Normal axis with normal T-waves	6	9	–
Normal axis with abnormal (diphasic or inverted) T-waves	5	9	–
Left axis deviation with normal T-waves	11	11	10
Left axis deviation with abnormal T-waves	9	20	26
Right axis deviation with normal T-waves	1	1	–
Right axis deviation with abnormal T-waves	1	4	2
	33	54	38

In left axis deviation (87 cases) RS-T depression was found without abnormal T-waves in 32 cases, or 37 per cent. In the remainder depression of the RS-T segment occurred in association with isoelectric, diphasic or inverted T-waves. The depression tended to be more marked in Lead I than in Lead II. Many curves showed, in addition, an elevation of the RS-T segment in Lead III. In most of these cases left axis deviation was well marked, and the QRS complexes were of high voltage and were often widened to 0.1 sec., especially when T_1 or T_1 and T_2 were inverted. This type of electrocardiogram, which is similar to that of left bundle branch block, is well known in cases of marked left ventricular preponderance.

In cases of right axis deviation the opposite was found, i.e., the depression of the RS-T segment was present in Lead III or in Leads II and III, and elevation, if any, was present in Lead I.

In 15 cases (52 per cent) in which there was neither right nor left axis deviation, depression of the RS-T segment occurred with normal T-waves in Lead I or II, or in both, and in three cases, in Leads II and III. When present in two leads the depression was more

marked in Lead II than in Leads I or III. In other cases the RS-T changes were generally in accord with the changes in the T-waves.

In 49 cases (38 per cent) chest leads were studied in addition to standard leads. Both depression and elevation were noticed, the latter being more frequent. It was found that depression was most marked in the apical lead, whereas elevation always increased the more the exploring electrode was shifted to the right of the precordium. In comparing the occurrence of deviations in standard and in chest leads it was found that these changes were more common in standard leads, and only in very few cases were they present in chest leads exclusively. It seems that chest leads are not helpful in revealing permanent depressions of the RS-T segment.

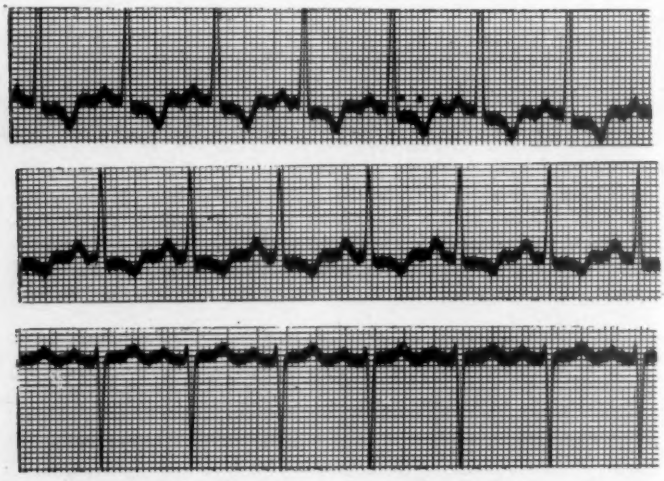

Fig. 1.—Left axis deviation with inversion of the T-wave in Leads I and II and depression of the RS-T segment in these leads. The RS-T segment in Lead III is slightly elevated. Clinically, a case of hypertensive heart disease with considerable enlargement of the left ventricle, proved by post-mortem examination.

C. CLINICAL INVESTIGATIONS

The data so far described were obtained from unselected electrocardiograms. They will now be considered in relation to the type of heart disease present.

1. *Hypertensive Heart Disease.*—Clinical, radiologic and electrocardiographic studies were made in 114 cases in which digitalis was not being given. These cases were divided into three groups, according to symptoms: A, No symptoms; B, slight to moderate effort dyspnea; C, left- or right-sided heart failure. In each group cases in which there was clinical evidence of coronary artery disease (angina pectoris or myocardial infarction) were considered separately. The results are presented in Table II, which reveals that depression of the RS-T

segment becomes more frequent with increase of signs and symptoms. The figures are 13 cases, or 45 per cent, with depression of the RS-T segment in Group A; 24 or, 52 per cent, in Group B; and 32, or 82 per cent, in Group C. The frequency of normal curves naturally declines in these groups: Group A, 52 per cent; B, 37 per cent; C, 7 per cent. A decrease in the incidence of curves in which the depression of the RS-T segment is the only abnormality can also be noted: Group A, 36 per cent; B, 25 per cent; and C, 10 per cent. It is therefore evident that the worse the state of the heart, the higher the incidence of abnormal electrocardiograms and the greater the degree of abnormality.

TABLE II

DEPRESSION OF THE RS-T SEGMENT IN THE THREE GROUPS OF CASES OF HYPERTENSIVE HEART DISEASE

TYPE OF ELECTROCARDIOGRAM	GROUP A				GROUP B				GROUP C			
	RS-T NORMAL		RS-T DEPRESSED		RS-T NORMAL		RS-T DEPRESSED		RS-T NORMAL		RS-T DEPRESSED	
	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA
Normal axis with normal T-waves	2	—	3	1	15	1	—	1	1	—	1	—
Normal axis with abnormal T-waves	—	—	2	—	2	2	2	1	—	—	2	1
Left axis deviation with normal T-waves	13	—	2	1	3	—	9	1	2	—	4	2
Left axis deviation with abnormal T-waves	1	—	4	—	1	—	7	3	2	—	17	5
Total	16	—	11	2	21	3	18	6	5	—	24	8

Comparing the anginal and nonanginal groups it can be seen that there were 19 cases (16.5 per cent) of hypertensive heart disease with angina pectoris, in 16 (84 per cent) of which depression of the RS-T segment occurred, whereas in only 53 (56 per cent) of the hypertensive nonanginal cases was this depression present.

2. *Aortic Valvular Disease.*—This group was divided into syphilitic cases with angina pectoris, syphilitic cases without angina, and nonsyphilitic cases in which angina did not occur. In the rheumatic group cases of mitral stenosis were excluded. Table III shows this comparison. The ratio of normal to depressed RS-T segments in the syphilitic nonanginal group was 2:11; in the syphilitic group with angina pectoris, 4:7; and in the nonsyphilitic group, 1:9. Thus the incidence of curves with the depressed RS-T segment was greater in the nonanginal syphilitic group than in cases with angina and was greatest in the nonsyphilitic group. These findings are important and will be discussed later.

TABLE III

COMPARISON OF SYPHILITIC AND NONSYPHILITIC AORTIC VALVULAR DISEASE

TYPE OF ELECTROCARDIOGRAM	SYPHILITIC AORTIC VALVULAR DISEASE WITHOUT ANGINA		SYPHILITIC AORTIC VALVULAR DISEASE WITH ANGINA		NONSYPHILITIC AORTIC VALVULAR DISEASE	
	RS-T NORMAL	RS-T DEPRESSED	RS-T NORMAL	RS-T DEPRESSED	RS-T NORMAL	RS-T DEPRESSED
Normal axis with normal T-waves	—	1	1	—	—	2
Normal axis with abnormal T-waves	—	2	1	1	—	2
Left axis deviation with normal T-waves	2	—	1	3	1	5
Left axis deviation with abnormal T-waves	—	8	1	3	—	—
Total	2	11	4	7	1	9

3. *Coronary Artery Disease.*—Twenty-five patients with angina pectoris or a history of myocardial infarction were examined (Table IV).

TABLE IV

DEPRESSION OF THE RS-T SEGMENT IN CORONARY DISEASE

TYPE OF ELECTROCARDIOGRAM	ANGINA PECTORIS		CORONARY OCCLUSION	
	RS-T NORMAL	DEPR.	RS-T NORMAL	DEPR.
Normal axis with normal T-waves	5	1	3	-
Normal axis with abnormal T-waves	1	1	1	-
Left axis deviation with normal T-waves	1	2	1	-
Left axis deviation with abnormal T-waves	2	2	4	1
Total	9	6	9	1

In 18 cases the RS-T segment was normal, and in seven it was depressed. When the groups of cases with angina and of cases with healed myocardial infarcts are studied separately, it can be noted that in the first group the ratio of normal to depressed RS-T segment was 9:6, and in the latter 9:1. In the second group 10 patients were studied who had had typical attacks of coronary occlusion from four months to two years earlier; the electrocardiograms showed evidence of old myocardial infarction of the Q_1T_1 type in 6 cases and of the Q_3T_3 type in 4 cases. In this group depression of the RS-T segment was present in only one case, and it should be noted that this case was complicated by aortic stenosis with considerable enlargement of the left ventricle.

Many patients of this group showed some enlargement of the left ventricle due to some complication such as hypertension, but in 10 out of 15 cases with normal RS-T segments the size of the heart was normal, whereas in the group with RS-T depression only 2 hearts were of normal size.

It is clear that in angina pectoris a depression of the RS-T segment is not uncommon, but in healed myocardial infarction it is very rare.

Other types of heart disease were not analyzed separately because of the rarity of the associated RS-T depression in the material examined.

4. *Relationship of Enlargement of the Heart to RS-T Depression.*—The size of the heart, especially of the left and right ventricles, was gauged by radiologic examination (radioscopy and teleoradiogram). Cases were classified and put into five divisions. Estimation of the size of the heart is not very easy and is subject to many errors, but all the patients were examined by the same observer (Dr. P. H. Wood). The results are shown in Table V.

TABLE V

RELATIONSHIP OF RS-T DEPRESSION TO ENLARGEMENT OF THE LEFT AND RIGHT VENTRICLES

	RS-T DEPRESSED	RS-T NORMAL
Left ventricular group:		
No enlargement	4 (31%)	9 (69%)
Slight enlargement	19 (43%)	25 (51%)
Moderate enlargement	21 (52%)	20 (48%)
Considerable enlargement	47 (90%)	5 (10%)
Gross enlargement	9 (100%)	-
Right ventricular group:		
Slight enlargement	3	5
Moderate enlargement	1	-
Gross enlargement	4	-

It is seen that the incidence of RS-T depression in Lead I increases as the size of the left ventricle increases and that the depression of that segment in Lead III runs parallel to the degree of right ventricular enlargement. Depression of the RS-T segment in Lead II was found to depend more upon deviation of the electrical axis than upon the size of the ventricles; it usually occurred with the lesser degrees of axis deviation.

5. *Post-Mortem Examinations.*—An autopsy was performed in 21 cases—11 cases of hypertensive heart disease, 2 cases of syphilitic aortic incompetence, 5 cases of primary coronary artery disease, 2 cases of mitral stenosis, and 1 case of cor pulmonale. The size of the ventricle was estimated, and the coronary arteries were carefully examined. Some of the cases will be included in a series shortly to be reported by Harrison and Wood, and in these the coronary arteries were examined by injections of a radiopaque substance.

Of the 11 hearts from patients who had had hypertension, 7 exhibited the unduly wide coronary arteries which are common in this disease (Harrison and Wood). Of these, 6 had gross left ventricular enlargement and the electrocardiograms of 5 had shown left axis deviation with depression of the RS-T segment in Lead I, or in Leads I and II with or without elevation of that segment in Lead III. In

other cases of hypertension the coronary arteries showed severe atheromatous changes causing irregularities of the outline with narrowing of the lumen. In these cases hypertrophy of the left ventricle was also gross, and the electrocardiogram had shown depression of the RS-T segment in Lead I in all of them.

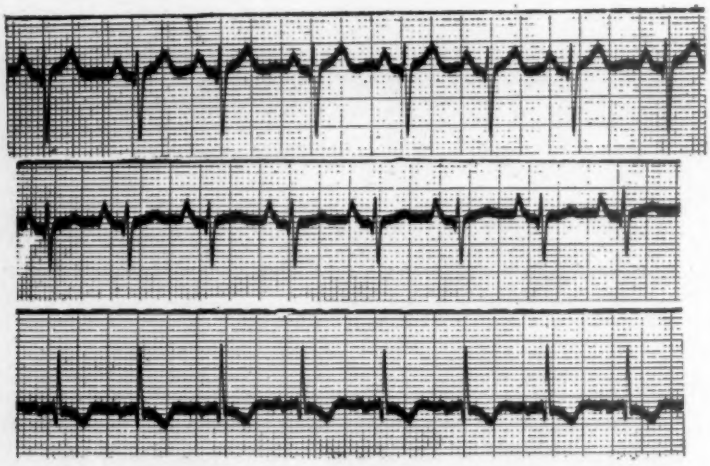

Fig. 2.—Right axis deviation with inversion of the T-wave and depression of the RS-T segment in Lead III and slight elevation of that segment in Lead I. Clinically, a case of chronic cor pulmonale with considerable enlargement of the right ventricle (post-mortem proof). Age of patient, 29 years.

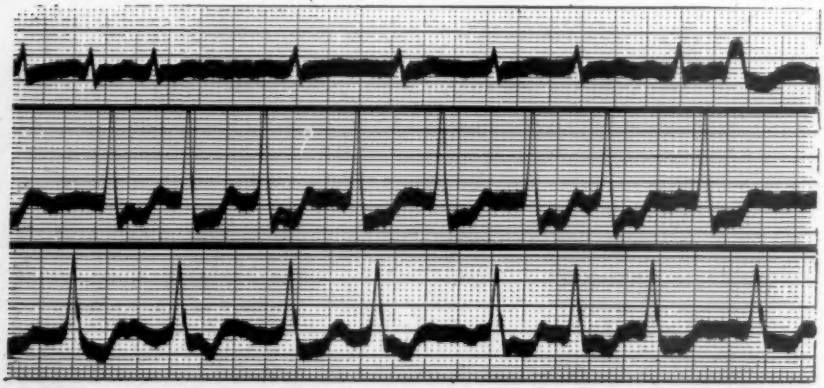

Fig. 3.—Normal electrical axis. Auricular fibrillation. Marked depression of the RS-T segment in Leads II and III. Clinically, a case of malignant hypertension with uremia, chronic bronchitis, and emphysema. Post-mortem examination showed considerable hypertrophy of the right ventricle (due to pulmonary disease) and only slight hypertrophy of the left ventricle.

In the 5 cases of occlusive coronary atheroma the left ventricle showed only slight if any hypertrophy. In 4 cases of this group there had been no abnormality of the RS-T segment in the electrocardiogram; in one a slight depression of the RS-T segment occurred in Lead I.

In both cases of syphilitic aortic incompetence the left ventricle was hypertrophied and the coronary ostia were markedly stenosed. In one case the electrocardiogram had been normal, and in the other there was a depression of the RS-T segment in Leads I and II.

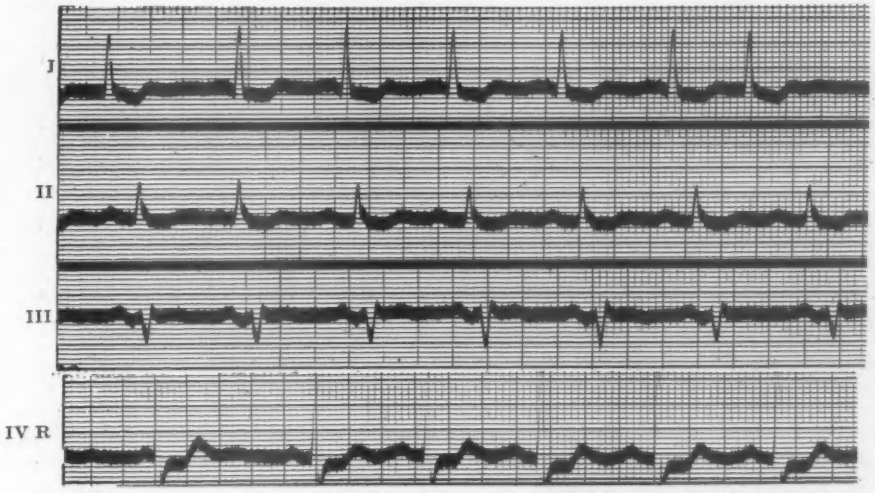

Fig. 4.—Left axis deviation with depression of the RS-T segment in Leads I and II and very marked depression of that segment in Lead IV R. Clinically, a case of hypertensive heart disease with moderate enlargement of the left ventricle (demonstrated radiologically).

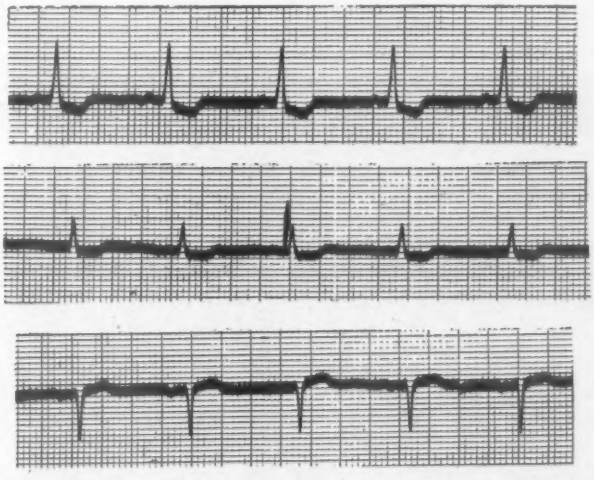

Fig. 5.—Left axis deviation with digitalis-like depression of the RS-T segment in Leads I and III and reciprocal elevation of that segment in Lead III. Clinically, a case of hypertensive heart disease with heart failure. No angina pectoris.

In the 3 cases of marked right ventricular hypertrophy the coronary arteries were normal (the oldest patient was 33 years old); the electrocardiogram had shown right axis deviation with a depression of the RS-T segment in Leads II and III.

IV. COMMENT

In discussing these results three questions are to be answered:

1. Is depression of the RS-T segment a definitely pathologic sign?

2. Does it occur as a specific change in one type of cardiac lesion only?

3. Are the deviations of the RS-T segment valuable as an aid in diagnosis?

1. The results of this study, which agree with those of other observers, show that deviation of the RS-T segment does not occur under normal circumstances in health. Temporary changes are not necessarily significant. They occur after violent exercise,[21b] in general anoxemia,[9] carbon monoxide poisoning,[19a] and as an effect of certain drugs,[14] but permanent changes do not occur unless disease of the heart is present.

2. The second question is more difficult to answer and must be considered more fully. From an etiologic point of view it has been shown that depression of the RS-T segment occurs in all types of heart disease. More important, however, is the anatomic site of the lesion. As no case of acute cardiac disease was included in this series, there are only two factors which have to be considered, namely, cardiac enlargement and occlusive coronary atheroma. Cases of predominantly left-sided heart disease were divided into three groups: enlargement without coronary artery disease, enlargement with coronary artery disease, and coronary artery disease with little or no enlargement. It is true that in most cases this division was made on the basis of clinical and radiologic examinations, without post-mortem control, and the clinical criteria for the diagnosis of coronary artery disease (angina, old cardiac infarction) are not very reliable, as there may be definite coronary disease without detectable signs and symptoms. The resulting figures, however, when examined critically, are of value. The incidence of RS-T depression in the first two groups does not differ materially. In the third group, in which coronary artery disease was established beyond doubt, the incidence of changes in the RS-T segment was found to be much lower than in the former groups. This was confirmed conclusively by the group of cases in which post-mortem examination was performed. On the other hand, it is seen that the incidence of deviation of the RS-T segment increases with the severity of the lesion and with the degree of the enlargement of the left (or right) ventricle. This relationship between left (or right) ventricular enlargement and the described changes in the electrocardiogram seems to be the most important result of these investigations. No relationship could be found between permanent depression of the RS-T segment and occlusive coronary atheroma. On the contrary, RS-T depression was less common

in angina pectoris and did not occur at all in uncomplicated cases of myocardial infarction in which coronary disease is certainly most advanced and severe.

As has been mentioned, certain authors believe that RS-T depression is a specific change in coronary insufficiency, but they place cardiac enlargement also in that category. It is a matter of opinion whether this is justified. It has been argued by T. R. Harrison[25] that the ultimate cause of heart failure in cardiac enlargement is probably anoxemia of the muscle, caused by the fact that blood cannot be delivered in sufficient amounts to the grossly hypertrophied organ. For theoretical reasons, perhaps, cardiac enlargement can be grouped with coronary insufficiency, but from the practical point of view I think that this cannot be accepted. Clinical and anatomic facts are against it. Uncomplicated hypertensive heart disease, which progresses almost invariably into left- and right-sided heart failure, is a typical clinical entity with clear-cut signs, symptoms, course, and prognosis and differs materially from ischemic heart disease. The same difference in symptoms and prognosis is seen between cases of syphilitic and rheumatic aortic valvular disease, although the anatomic findings, apart from those in the coronary arteries, are identical. It has been mentioned that Harrison and Wood found in uncomplicated cases of hypertensive heart disease enlarged coronary arteries with increased vascularity of the hypertrophied muscle, whereas in other cases the arteries were narrow and irregular and the vascularity poor.

These two entities, therefore, are entirely different diseases and cannot be considered together in a common group.

The great progress in cardiology is to some extent due to modern classification of heart disease, mostly by American authors (*Criteria for the Classification and Diagnosis of Heart Disease*, ed. 3, 1931) and to use the term "coronary insufficiency" to include both groups would be a retrograde step.

The second question, therefore, can be answered by saying that depression of the RS-T segment is very closely related to enlargement of one of the ventricles, although it is not a specific sign of this abnormality. It occurs in left ventricular enlargement in Lead I and in right ventricular enlargement in Lead III.

3. It has been shown that depression of the RS-T segment occurs in all types of heart disease. In advanced stages it is more marked and is as a rule accompanied by changes in the T-waves. In considering the relationship of the changes in the RS-T segment to the changes in the T-waves, it is to be noted that they both occur in similar conditions. Any factor which causes temporary RS-T deviation (angina pectoris, coronary occlusion, digitalis, anoxemia, etc.) affects also the T-waves, if not simultaneously, then at a later stage. It is highly probable that persistent changes in these two parts of

the electrocardiographic curve are also of the same nature, caused by the same process. Therefore, if both changes are found in the same electrocardiogram, the diagnostic value of the deviation of the RS-T segment is limited because changes in the T-waves are more conspicuous and more readily recognized. There are, however, cases in which deviation of the RS-T segment can be of some help in the diagnosis. It has been shown that in electrocardiograms with axis deviation there are often a depression and an elevation of the RS-T segment in the two opposed leads, i.e., deviation in the opposite direction to the main QRS complex. This occurs most frequently in cases in which there is already electrocardiographic evidence of considerable enlargement of one of the ventricles, i.e., marked axis deviation with high voltage and slight prolongation (up to 0.1 sec.) of the QRS complex and T-waves in the opposite direction to the main ventricular complex. But in a number of cases changes in the RS-T segment occur earlier than QRS and T changes. It has been stated that depression of the RS-T segment in one lead and elevation in the opposed lead occur only when there is an enlargement of one ventricle, and this may be of value. Left axis deviation can be caused by several factors and does not necessarily mean left ventricular enlargement, but left axis deviation with depressed RS-T_1 and elevated RS-T_3 means moderate to considerable enlargement of the left ventricle. It has the same meaning as if T_1 were inverted and T_3 upright. The same statement applies to right axis deviation, i.e., right axis deviation with depressed RS-T_3 and elevated RS-T_1 means predominant enlargement of the right ventricle.

There is another group of cases in which RS-T deviation can be of diagnostic value—cases in which more than one factor is influencing the electrocardiographic curve. It happens not infrequently that there is no abnormal axis deviation when one would expect it to be present; this may be the resultant of two opposing factors, such as mitral and aortic valvular disease, hypertension and a low position of the diaphragm, etc. In some of these cases the RS-T segment is depressed in two leads, and this may be of help; a normal position of the electrical axis with depression of the RS-T segment in Leads I and II means that the left side of the heart is mainly affected, whereas a depression of that segment in Leads II and III means that the right side of the heart is the more involved.

I hope to be able to show in a subsequent paper that this statement applies not only when there is a persistent depression of the RS-T segment, but also when this depression is caused by digitalis. This widens the diagnostic value of this observation, as distortion of the electrocardiogram caused by digitalis is very common, and in many cases in when there is no axis deviation and the drug causes a conspicuous depression of the RS-T segment, the lead in which this effect occurs may indicate the chamber which is most enlarged.

Last, there is a group of cases in which the depression of the RS-T segment is the only abnormality of the electrocardiogram. It has been said that such a depression is definitely abnormal and therefore that electrocardiograms in which it occurs are to be considered as indicating disease. Although most often associated with cardiac enlargement, depression of the RS-T segment has, in common with an abnormal T-wave, a manifold meaning. Generally it can be considered as a forerunner of a T-wave inversion. In the material examined it was found that in early cardiac disease depression of the RS-T segment occurs as the only abnormality of the electrocardiogram, but in more severe cases it is likely to be combined with abnormal T-waves. This seems to justify the statement that a depression of the RS-T segment is an early abnormal sign having the same significance as a pathologic T-wave (with the exception of old cardiac infarction) and that, when it appears, changes in the T-waves are to be expected.

As stated above, the diagnostic value of the chest leads in detecting early changes of the RS-T segment in the electrocardiogram is limited.

V. CONCLUSIONS AND SUMMARY

1. A persistent depression of the RS-T segment in the electrocardiogram is an abnormality of importance.

2. It is usually most marked in the lead in which the main ventricular complex shows the maximum upward deflection. In some cases there is an elevation of the RS-T segment in the opposed lead, i.e., when there is depression in Lead I, there may be elevation in Lead III, and vice versa. The elevation, however, is a later and less important change.

3. Depression of the RS-T segment is most often associated with enlargement of the left or right ventricle and usually occurs as a forerunner of T-wave inversion. It occurs in left ventricular enlargement in Lead I, or in Leads I and II; in right ventricular enlargement it is found in Lead III, or in Leads II and III. Usually it is found in conjunction with right or left axis deviation, but it has the same significance in curves in which there is no abnormal deviation of the axis.

4. The statement of many German authors that the depression of the RS-T segment is a specific sign of coronary insufficiency is not confirmed.

I wish to express my thanks to Prof. F. R. Fraser and to Dr. P. H. Wood for their criticism and help in preparation of this article. I am indebted to Sir Frederick Menzies, Chief Medical Officer of the London County Council, for his permission to utilize the material of the hospital.

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FURTHER OBSERVATIONS ON APICAL SYSTOLIC MURMURS IN CHILDREN*

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IN 1932 we published a paper[1] in which we reported the results of our study of apical systolic murmurs in 100 children whom we had followed for six or more years. At that time we observed that (1) 30 per cent of the children developed severe organic heart disease (mitral stenosis, aortic insufficiency, or both); (2) 50 per cent of those who gave a history of rheumatic fever or chorea developed serious organic heart disease; (3) among those who had physical signs of enlargement of the heart at the first examination, 37 per cent developed serious organic heart disease; (4) of those whose cardiac enlargement was demonstrated by means of the orthodiagram, 40 per cent developed serious cardiac disease; (5) only 9 per cent of those whose hearts were entirely normal fluoroscopically developed further evidences of cardiac disease; (6) in only 8 per cent of the patients did the murmur disappear completely; (7) only one of the seven patients who were five years of age or under developed organic heart disease, and this patient had an attack of chorea when she was eight years old, following which she developed mitral stenosis; (8) the electrocardiogram seemed to be of no value in estimating the prognosis.

As considerable time has elapsed since the original study was made, we thought it advisable to re-examine as many of the patients as possible in order to get a still better idea of the significance of apical systolic murmurs in children. In the present report only patients who have been followed for ten years, or more, are included. The series is not very large because it is difficult to follow young people in a clinic for more than ten years; they grow up and leave town, marry, or become prosperous and are lost sight of. However, since those who are not doing well are usually the ones who keep in touch with the clinic, our statistics tend to paint a picture which is somewhat too gloomy.

We have been able to follow 33 (15 males and 18 females) of the original 100 patients for ten years, or more.† The period of observation ranged from ten to sixteen years, averaging more than twelve years. Seven of the patients had mitral stenosis alone, one had aortic

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†Since 1932, one death has been reported to us. The patient was a girl whom we had followed for seven years. She died at the age of 15 of subacute bacterial endocarditis. This was the second fatality known to have been caused by subacute bacterial endocarditis in the original group of 100 patients.

insufficiency alone, and one had both mitral stenosis and aortic insufficiency. This makes a total of nine patients (27 per cent) who developed serious valvular heart disease. At the time of our first study this proportion was about the same (30 per cent). In four cases (12 per cent) the murmur had disappeared entirely; this occurred in 8 per cent of the original series. Twenty of the 33 patients (61 per cent) still had systolic murmurs, and nothing more; this is exactly the same proportion as in the group of 100. No new cases of mitral stenosis or aortic insufficiency had developed since the previous study. Therefore, our original statement that mitral stenosis was first diagnosed between one and nine years (average 4.7 years) after the discovery of a systolic murmur is still valid. Aortic insufficiency occurred somewhat earlier; the diagnosis was made, on the average, within three years after discovery of the systolic murmur.

In our previous study we had tried to ascertain whether the presence of fever had any prognostic significance, and at that time we considered an oral temperature of 99° F., or above, on at least two successive visits, as evidence of fever. However, we found that most of our patients had such temperatures at one time or another, and concluded that this was of no prognostic significance. In our present series it was found that, according to this standard, 75 per cent of the patients had fever. When we made our criteria of fever more strict, and considered only temperatures of 99.6° F., or above, on three successive visits, as significant, we were still unable to draw any conclusions, for only one patient's temperature exceeded this limit. However, it must be remembered that we were dealing only with ambulatory patients who might not have been brought to the clinic at times when their temperatures were elevated. For the purpose of ascertaining accurately the prognostic significance of fever it will probably be necessary to have the temperatures taken daily at home. Nevertheless, our observations indicate that a slight elevation of temperature (between 99 and 100° F.) does not appear to have any prognostic significance.

Unfortunately, the blood pressures of children and young adults were not measured routinely in our clinic, so that we have blood pressure data in only eight cases. Four of these patients showed a tendency to hypertension at an early age (a patient with mitral stenosis had a blood pressure of 140/100 at the age of 20 years, and three patients with only systolic murmurs had pressures of 160/84, 140/80, and 140/90, at the ages of 21, 20, and 27 years, respectively). The question of the development of hypertension in patients who had systolic murmurs in childhood might be worth further investigation.

CONCLUSIONS

1. Of 33 children with apical systolic murmurs who were followed for more than ten years, 27 per cent developed serious valvular heart

disease (chiefly mitral stenosis), 61 per cent still had systolic murmurs and nothing more, and 12 per cent lost their murmurs entirely.

2. Those who developed mitral stenosis did so between one and nine years (usually between four and six years) after the discovery of the original murmur.

3. Slight elevation of temperature in children with apical systolic murmurs is of no significance as a prognostic sign.

4. There is a possibility that children with apical systolic murmurs have an abnormal tendency to develop early hypertension.

5. Conclusions drawn after following 100 children with systolic murmurs for six years[1] were unshaken by following 33 of the same children for an additional period of four years, or more.

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PANCREATIC NECROSIS ASSOCIATED WITH AURICULAR FIBRILLATION AND FLUTTER

Report of a Case Simulating Coronary Thrombosis (Autopsy Findings)*

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PANCREATIC necrosis associated with auricular fibrillation has been found but once in an exhaustive survey of the literature.[1] In that instance Drummond observed a rapid, complete arrhythmia in a case of pancreatitis which disappeared after the acute attack had subsided.

Nothnagel,[2] in 1876, enumerated the various extracardiac causes of arrhythmia and dwelt particularly upon the comparatively small group of individuals who had arrhythmias and apparently normal hearts. Orgain, Wolff, and White[3] have recently (1936) reviewed this entire subject, classifying the various extracardiac causes of auricular fibrillation and auricular flutter as found in the literature.

The rarity of pancreatic necrosis causing auricular fibrillation, the cardiac nature of many of the patient's complaints with confirmatory physical findings and laboratory analyses, and the complete post-mortem study have prompted the following report.

CASE REPORT

J. P., No. D1627-37, a 53-year-old bartender of Czechoslovakian birth, was first seen by one of us (E.L.D.) March 16, 1937, four hours after the onset of sharp upper abdominal pain, of a constant burning character, following indiscretions both in eating and drinking. Associated symptoms included gaseous eructations, nausea, orthopnea, and substernal oppression. The patient had had somewhat similar, although very much milder, experiences two years, one year, and five days before, respectively. Since the first of these attacks associated with abdominal pain radiating to the right shoulder, which confined him to bed for only one day, he had suffered from dyspnea on slight exertion but had shown no other signs of congestive heart failure.

The patient's past history included measles, whooping cough, and bronchopneumonia in childhood, typhus fever at the age of 19 years, and chronic bronchitis for the past ten to fifteen years; he attributed the latter to the fact that he was accustomed to smoke forty to sixty cigarettes daily. He drank heavily of both coffee and beer.

Physical examination revealed an orthopneic, cyanotic, cold, clammy, obese, extremely restless individual, seated on the edge of the bed, apparently in severe pain and holding his upper abdomen firmly. The rectal temperature was 99° F. His face was ashen, his lips blue, and his entire body bathed in a cold perspiration. Examination of the mouth revealed a coated tongue, a foul breath, and a number of carious teeth. There were no abnormal pulsations in the neck, and no engorgement of the cervical veins was noted. The lungs were negative except for occasional coarse

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TABLE I
LABORATORY FINDINGS

	3/16	3/17	3/18	3/22	4/2	4/3	4/7	4/8	4/10	4/16	4/19	4/23
Blood Count:												
Hb. (%)	106				80							80
R. B. C.	5.09				4.31							4.15
W. B. C.	19.9				22.2	21.8		14.5		13.2		11.3
Neutrophiles	83				87	81		72		88		77
(Mature)	(71)				(62)	(51)		(37)		(48)		(34)
(Immature)	(12)				(25)	(31)		(35)		(40)		(43)
Lymphocytes	17				10	4		25		12		18
Eosinophiles						2						
Monocytes					3	13		3				3
Myelocytes												2
Anisocytosis						Marked						
Polychromatosis						Moderate				Slight		
Macrocytosis						Moderate						
Microcytosis						Moderate						
Achromia										Slight		
Icteric Index				20.2					10.6			
Sedimentation Rate:												
mm. in hr.	2		17			20						
cell vol. %	68		52			52						
Blood Chemistry (mg. %):												
N.P.N.		45.1									27.9	
Urea				19.0					13.5			
Creatinine				1.76					1.36			
Protein (Total mg. %)					8.59							
Chloride											396	
CO_2 combining power (vol. %)											68	
Feces:												
Neutral Fat					Small amount					Very slight amount		
Fatty Acid					Many crystals					Occasional crystal		
Soaps					None					None		
Urinary Diastase							32		20		11	

râles heard over both lower lobes posteriorly. The apex beat of the heart was located in the fifth interspace, one inch to the left of the midclavicular line. There were no thrills. The auricles were fibrillating and the ventricular rate was 120 a minute, but there was no pulse deficit. The intensity of the aortic second sound was normal. No murmurs were heard. The blood pressure was 160/90. The abdomen was markedly obese and diffusely tender, but actual muscular spasticity was absent. The liver edge was palpable three fingerbreadths below the costal margin. The extremities showed no edema.

On admission to the hospital six hours later, after ¾ gr. of morphine sulfate in divided doses had failed to relieve his pain, the patient's status was little changed save that the blood pressure had fallen to 120/80, his rectal temperature had risen to 102° F., and his abdominal tenderness seemed more localized in the right upper quadrant.

Laboratory procedures with the exception of blood and urine sugar determinations are summarized in Table I. The latter are recorded in connection with dietary changes and insulin administration in Table II. The urine on the day of admission

TABLE II

SPECIAL RECORD: CASE NO. D1627-37

DATE	DIET		INSULIN UNITS	URINE			BLOOD SUGAR (MG. %)	GLUCOSE INTRAVENOUSLY	
	TYPE	CALORIES		ACETONE	SUGAR BENEDICT'S QUAL. SOL.	DIACETIC ACID		AMOUNT C.C.	CONCENTRATION %
3/16	Karell	800	0		Trace			50	25
								100	50
3/17	Karell		0		Trace		206.4	50	50
3/19	Carbohydrate 100	800	0		Trace				
3/22	Protein 60		0				375		
3/23	Fat 26		15-0-10		Trace				
3/24			15-0-10	Absent	Green	Absent			
3/25			15-0-10	Absent	Green	Absent	200		
3/27	Light		0				248		
3/28			0	Absent	Green	Absent			
3/29			0	Absent	Green	Absent			
3/30			0	Absent	Blue	Absent			
3/31			15-0-10	Absent	Blue	Absent		200	10
4/1			15-0-10						
4/2	Buttermilk		15-0-10				210.6	50	50
4/3			15-0-10		Blue			500	10
4/5			15-0-10					500	10
4/6			15-0-10					500	10
4/7			15-0-10					500	10
4/8	Light, variable		15-0-10		Blue			500	10
4/9	Negligible		15-0-10					500	10
4/10			15-0-10				157.4	500	10
4/11			15-0-10					1000	10
4/12			15-0-10		Blue			1000	10
4/13			15-0-10					1000	10
4/14			15-0-10					1000	10
4/15			15-0-10					1000	10
4/16			15-0-10		Yellow			1000	10
4/17			15-0-10					1000	10
4/19							193.6		

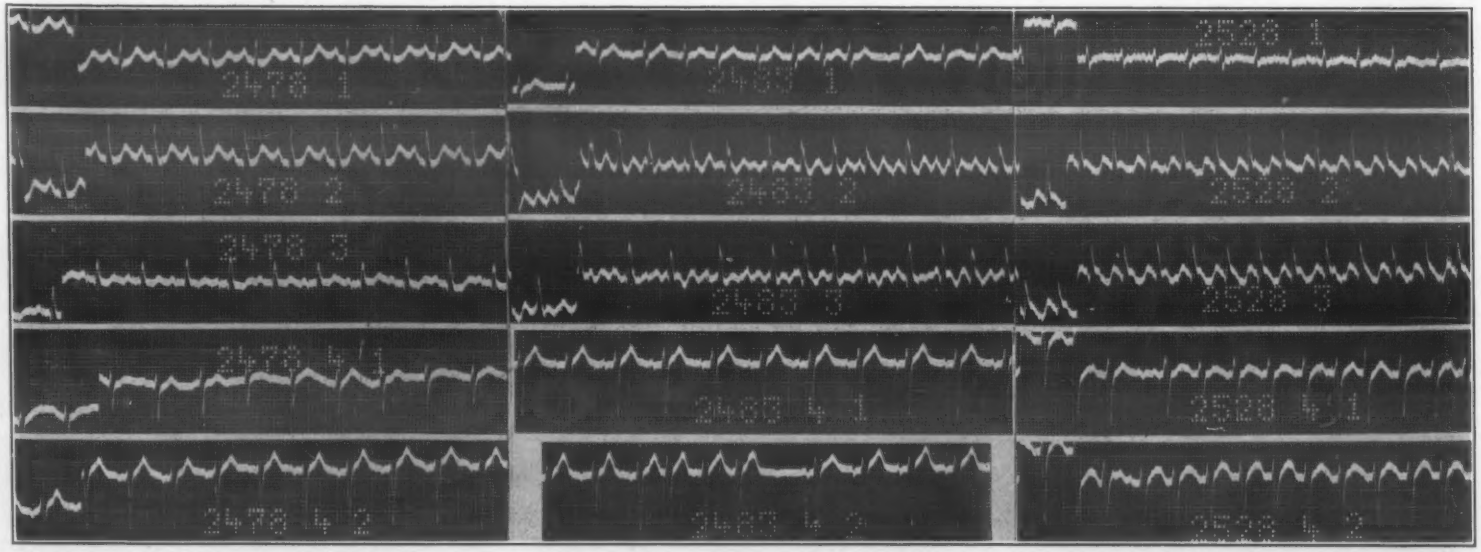

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—On admission, March 16, 1937, pulse rate 120, slowing of R, II, and thickening of R, IV-1,* are suggestive of some difficulty in spread of excitation wave through the ventricles, but there is no evidence of any frank intraventricular conduction defect as QRS time is not prolonged.

Fig. 2.—On March 18, 1937, Leads I, II, and III show impure flutter with rate of 390. Auriculoventricular block constantly varies, producing completely irregular ventricular beats. Average ventricular rate is 130 to 150. The ventricular complexes show some slurring and notching; there is no axis deviation. Lead IV-1 shows the normal sinus mechanism, rate 110, no conduction defects. Lead IV-2 shows two periods of irregularity, one due apparently to an auricular premature contraction and the other probably due to fibrillation. Conclusion: Impure flutter and fibrillation of paroxysmal type with rapid ventricular rate.

Fig. 3.—On April 3, 1937, the auricular oscillations were large and fairly regular and represented impure flutter rather than fibrillation; average ventricular rate, 160

*In Leads IV-1 and IV-2 the left electrodes are placed anteriorly.

showed a trace of albumin and of sugar and a few granular and hyaline casts, a few leucocytes, and several erythrocytes per high power field. The hemoglobin content was 106 per cent; the erythrocytes numbered 5,909,000, and leucocytes 19,900 per c.mm.; 71 per cent of the latter were mature polymorphonuclear cells, 12 per cent immature polymorphonuclear forms, and 17 per cent lymphocytes. Subsequent blood counts (Table I) showed a persistent leucocytosis of varying degree with the percentage of immature polymorphonuclear neutrophiles steadily rising until April 23, 1937, three days before death. The sedimentation rates ranged from 2 mm. in one hour on admission to 20 mm. in one hour during the third week of illness. Blood sugar determinations routinely yielded a high value, but showed a normal type of response to insulin therapy, as did also the urine sugar (Table II). With the exception of nonprotein nitrogen, which was slightly elevated on admission and subsequently returned to normal, all other blood chemical analyses were within usual limits (Table I). Serial electrocardiograms taken on March 16, March 18, and April 3, 1937 (Figs. 1, 2, and 3) showed varying degrees of auricular flutter of an impure type, slurring of the R-waves, and occasional extrasystoles. These changes were taken to indicate posterior myocardial infarction.

Clinically, the early course of the patient in the hospital definitely suggested that he had had coronary thrombosis. However, upper abdominal pain, burning, moderate fever, and diffuse tenderness persisted. Even small amounts of fluid food produced nausea and vomiting and, with the exception of milk, seemed to intensify the burning. Despite the diffuse abdominal tenderness there was very little rigidity, but towards the end of the second week of his illness, distention became marked and a small amount of free fluid could be detected in the flanks. Simultaneously, slight edema of the ankles and coarse râles at the bases of both lungs were noted. Moreover, cardiac irregularity, low blood pressure (110/80), and the electrocardiogram seemed to confirm the presence of coronary occlusion. In conjunction with the abdominal symptoms an intractable, profuse, very watery, offensive diarrhea supervened. Stool examination (Table I) indicated an increasing inability to digest fats. Urinary diastase was within normal limits on three occasions (32, 20, and 11 units, respectively). The patient grew worse progressively, with marked intensification of all abdominal phenomena and an exacerbation of fever during the four days preceding death on April 26, 1937.

*Autopsy** findings in the heart and pancreas may be summarized as follows:

The pancreas was found to be diffusely converted into a soft, dirty, grayish-brown, chalky mass resembling a sequestrum. Where the pancreas touched the duodenum a perforation, about 1 cm. in diameter, was found in the mesial wall of the duodenum. The tissues in this region were soft and gangrenous. This cavity communicated with the greater peritoneal sac through a perforation in the posterior peritoneum behind the duodenum. A similar perforation was seen in the wall of the colon which formed one side of this cavity.

Microscopically, the pancreas showed complete autolytic necrosis. The surrounding connective and fat tissue showed hyperemia, edema, and cellular infiltration. In other sections, coagulative and ischemic necrosis was present together with considerable precipitated blood pigment.

The heart weighed 450 gm. There was a moderate amount of free, contracting, "chicken-fat" clot in the right ventricle and auricle. The cardiac muscle was soft and flabby, pale red in color, and uniform in appearance throughout. A moderate amount of fat tissue was present beneath the epicardium. Both coronary arteries were patent throughout and on section presented smooth, intact intimae. The left

*Performed by Drs. W. E. Youland and G. Nagamatsu.

coronary artery presented a few miliary, flat, whitish plaques. Several small atheromatous plaques were seen in the ventricular endocardium near the aortic valve.

Serial microscopic sections taken from the interventricular septum showed an hypertrophy of the muscle fibers throughout. Multiple sections from each ventricle, including the coronary vessels, valvular cusps, and myocardium, showed a uniform degree of muscular hypertrophy, together with little if any myocardial fibrosis. One coronary vessel presented at its base slight to moderate fibrotic thickening of the intima and subintima, without calcific or obliterative changes.

The anatomicopathological diagnoses included: chronic obesity with myocardial hypertrophy; complete coagulative necrosis of pancreas with sequestration and massive fat necrosis of omentum, mesentery, and peritoneum (apparently cause of death); massive phlegmonous and gangrenous inflammation of retroperitoneum and lesser omental cavity communicating with the greater peritoneal cavity; gangrenous perforation of duodenum and colon; generalized serofibrinous peritonitis; cholelithiasis.

DISCUSSION

In retrospect, it is not difficult to trace the course of this acute gangrenous pancreatitis from its predisposing causes—obesity, alcoholism, and gallstones—through a series of attacks of acute indigestion closely following heavy eating and drinking, to a conclusion in the severe episode that constituted the patient's last illness. Careful analysis shows that the important features of acute pancreatic disease, as summarized by Deaver[4] and, more recently, by de Takats,[5] could be demonstrated in this patient. Nevertheless, certain aspects of the case warrant particular comment:

1. *The Cardiac Phenomena.*—A diagnosis of coronary occlusion was made clinically in view of the orthopnea, substernal as well as epigastric distress, the cardiac irregularities (which had never been present before), and the configuration of the electrocardiographic tracings. Indeed, in the first few days of his illness these phenomena, in conjunction with the nausea and vomiting, cyanosis, moderate rise in temperature, glycosuria, hyperglycemia, and leucocytosis, cast doubt upon the possibility of any other disease. Autopsy revealed the incorrectness of such a conclusion; all of the symptoms must have resulted from the intra-abdominal condition.

Among the intra-abdominal causes of functional cardiac disturbances, diseases of the gall bladder and biliary tract have long been conceded a first place. Biliary colic and its associated digestive disturbances may produce cardiac murmurs, tachycardia, bradycardia, arrhythmia, cardiac pain, and dyspnea.[6-17] Typical cardiac angina with radiation of pain to the left arm has been observed in hepatic[13, 18] and gastrointestinal disease.[8, 17-22]

Almost any and all of the inflammatory states, particularly those, such as ruptured peptic ulcer, which are associated with shock, have been noted to produce cardiac disturbances reflexly.[23] In the present

instance pancreatic necrosis, multiple intestinal perforations, and widespread peritonitis were all present. However, inasmuch as the cardiac dysfunction appeared early it seems logical to attribute it primarily to the pancreatic disease. Auricular fibrillation occurring in a normal heart as a complication of proved acute pancreatitis, as aforesaid, has been reported in the literature but once.[1] The present case is the first in which autopsy established with certainty the structural normality of the heart. This point seems to be of considerable importance, as it is known that subdiaphragmatic lesions not infrequently initiate cardiac symptoms when the heart is already damaged.[24-26] For instance, cholecystitis and arteriosclerotic heart disease exist in the same age group, but clinical evidence of the cardiac changes may be absent until an acute exacerbation of the gall bladder condition occurs.[26, 27] Moreover, in such a situation the removal of the gall bladder may relieve the cardiac symptoms, as, for instance, the angina pectoris.[17, 18, 28]

2. *The Disturbance in Carbohydrate Metabolism.*—Statistical proof of the frequent association of temporarily disturbed carbohydrate metabolism and coronary occlusion has been furnished by a number of workers.[29-32] Raab and Rabinowitz[32] found abnormal sugar tolerance curves in all cases of coronary occlusion during the first two weeks of illness. In the present instance the moderate hyperglycemia and slight glycosuria on admission were attributed directly to coronary occlusion. They could have resulted from (a) pain and shock (Levine[29]), (b) reflex spasm of the already diseased pancreatic blood vessels (Cruickshank[33]), or (c) the edema of the medulla and lower pons which Hausner and Hoff[34] have found early in coronary thrombosis. The last mentioned workers believe this transudation produces a disturbance of the vegetative nervous centers of the brain, resulting in glycosuria and hyperglycemia. Later events showed that in our case none of these mechanisms was involved and that the abnormality in carbohydrate metabolism was entirely of pancreatic origin. At autopsy no normal insular tissue could be found. In view of this it is rather remarkable that only twenty-five units of insulin sufficed to keep the patient sugar-free and at one time brought the blood sugar within the range of normal. The concomitant absence of acetonuria and the presence of obesity might suggest a lowered activity of the pituitary gland, which unfortunately could not be investigated post mortem.

3. *The Low Urinary Diastase.*—Whether diastase excretion values are high or low in pancreatic disease would seem to depend chiefly upon the relative degrees of obstruction and necrosis present. High degrees of duct occlusion would naturally produce very high values, whereas advanced destruction would give rise to normal or extremely low values. The significant feature in the present instance seems to be the continuously decreasing value which could be looked upon as a measure of the progression of pancreatic disintegration.

4. *The Role of the Gall Bladder Disease in Precipitating the Acute Pancreatitis.*—Obvious chronic pathologic changes were present in the gall bladder; it seems likely that temporary lodgment of a small stone at the ampulla, associated with heavy eating and drinking, could have initiated the entire disturbance. Some years ago Opie[35] demonstrated the causative role of such an accident. Although the duct of Wirsung could not be isolated with any certainty because of the advanced necrosis, the common bile duct showed inflammatory changes of an acute nature near its entrance into the duodenum. It seems reasonable to suppose, therefore, that the cholecystic disease and the pancreatic necrosis were causally related. The late increase in the icteric index can be accounted for on the grounds of edema accompanying a spreading inflammatory process.

SUMMARY

1. A case of acute pancreatic necrosis presenting impure auricular flutter and fibrillation is reported. The rarity of the condition and its clinical similarity to coronary thrombosis are stressed.

2. The autopsy failed to disclose any organic changes in the heart to account for the arrhythmia; it was probably initiated by reflexes originating within the abdomen.

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Department of Clinical Reports

JUVENILE RHEUMATIC FEVER

Report of a Case in an Infant Two Years of Age

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ALTHOUGH rheumatic fever in infancy is unusual, the literature nevertheless contains a number of reports of authentic cases. Our present views regarding the incidence of first attacks differ considerably from those which were held even a decade ago. As Roth, Lingg, and Whittemore[1] have pointed out, "acute rheumatism in children has its onset at a far earlier age than is generally implied in the literature on the subject. If in coming years our familiarity with the 'minor' symptoms and signs of juvenile rheumatism becomes greater, and if dependable diagnostic tests come to our aid, the disease may be found to have its onset among the earliest diseases of childhood."

CASE REPORT

The patient was a white male child, 32 months of age, the fourth of four living children. None of the other children and neither of the parents had had rheumatic fever. It is perhaps significant that about a year before the patient was born his parents suffered serious financial reverses which forced them to remove to a small, inadequately heated apartment. Throughout her pregnancy the mother was denied all but the bare necessities, and the surroundings were unfavorable for the baby. Nevertheless, he appeared to be unusually well and strong until the onset of his rheumatic fever. He was not subject to colds, had not had tonsillitis, sore throat, or pains in the extremities, and was never listless, pale, or easily fatigued.

When first seen, the patient was acutely ill. He was sitting up in bed gasping for air and breathing very rapidly with a loud expiratory grunt. His face and extremities were cyanotic, cold, and clammy. The child had caught cold for the first time, and had been treated at home for one week prior to his admission, May 5, 1937, to the Orange Memorial Hospital. The diagnoses on admission were (1) bilateral otitis media, (2) pharyngitis, and (3) bronchopneumonia. On May 9, when the patient appeared quite "toxic," hemolytic streptococci were recovered from his throat. At this time the hemoglobin was 60 per cent (Sahli), the erythrocytes numbered 3,240,000, and the leucocytes 14,000, per cubic millimeter, respectively; 62 per cent of the leucocytes were polymorphonuclear cells and 38 per cent were lymphocytes. Roentgenograms taken on admission showed bronchopneumonia, chiefly in the lower lobe of the left lung, and a cardiac shadow the contour of which was suggestive of congenital heart disease. On May 11 the hemoglobin was 55 per cent, the erythrocyte count 2,800,000, and the leucocyte count 17,100; 42 per cent of the leucocytes were polymorphonuclear cells and 58 per cent were lymphocytes. The sedimentation rate was 14 mm. in thirty minutes and 35 mm. in one hour. The urine was normal. On May 14 the temperature was normal and the pulse "somewhat irregular and quite high." There were roentgenographic changes suggestive of miliary tuberculosis, but the Mantoux test was negative in all

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dilutions. On May 17 a transfusion of 120 c.c. of whole blood was given, and the next day the hemoglobin was 68 per cent, the erythrocyte count 3,780,000, and the leucocyte count 9,100. The differential leucocyte count showed 54 per cent polymorphonuclear cells, 44 per cent lymphocytes, and 2 per cent monocytes. On May 20 the temperature was still normal and the pulse somewhat irregular. Roentgenographically, there was continued evidence of miliary tuberculosis, but the bronchopneumonia appeared to be resolving. Stomach washings were examined for tubercle bacilli, but none was found. On May 25 the patient was discharged from the hospital with a final diagnosis of nasopharyngitis and bronchopneumonia. A diet high in calories and vitamins was prescribed.

A month later the patient again became acutely ill, but the clinical aspects of the case now differed considerably from those which had characterized his first illness. He had passed no urine for twenty-four hours. His breathing was labored and rapid (60 respirations a minute) and there was now only a slight grunt. He was not cyanotic, as he had been before, but pale, and his face was somewhat swollen. There was moderate edema of the legs and lower thighs. The abdomen was distended and tympanitic, and the liver was greatly enlarged, extending almost to the symphysis pubis. Many moist râles were heard over both lungs, but there was no dullness to percussion. At the apex of the heart there were loud systolic and diastolic murmurs which were transmitted over the entire precordium and could be heard very distinctly in the left axilla and under the left scapula. In addition, there was a suggestion of a diastolic murmur in the aortic area. No pericardial friction rub could be heard. The vessels of the neck pulsated violently. A poor prognosis was given, and immediate hospitalization advised.

The patient was admitted to the East Orange Homeopathic Hospital June 2, 1937. He was placed in an oxygen tent, his fluid intake was limited to 500 c.c. in twenty-four hours, and he received ammonium chloride (60 grains a day), salyrgan, and codeine every three or four hours when necessary. He began to pass urine almost at once, his liver receded, the edema of his extremities diminished, and his breathing became much easier. After forty-eight hours the ammonium chloride was discontinued, and he was given 2 c.c. of digalen hypodermically three times a day for three days. He also received one more intravenous injection of salyrgan. He responded so well that by June 9 the liver was only about one fingerbreadth below the costal margin, the peripheral edema had disappeared entirely, and the lungs were free of moisture. On June 19, when he walked out of the hospital, he had recovered completely from his cardiac failure, but his heart was still tremendously enlarged (Danzer ratio 0.75). It is noteworthy that his urine had remained normal throughout and that his sedimentation rate had never exceeded 11 mm. in one hour. The hemoglobin varied between 59 and 62 per cent, and the erythrocyte count was about 3,500,000 per cubic millimeter.

The patient's mother was advised to take him to the shore for the summer, to limit his physical exertion, and to give him frequent sun baths and a diet high in calories, vitamins, and iron. These instructions were carried out and he did very well. On his return, September 1, 1937, examination revealed no peripheral edema or other evidence of cardiac failure. The size of the heart had not changed appreciably, and the murmurs were the same as before. The heart sounds were of good quality and sinus arrhythmia was present. The blood pressure could not be measured accurately. There was no dyspnea on moderate exertion. The patient's appetite was excellent, and on the whole he presented a very healthy appearance.

On October 2, 1937, he again caught a "cold" which did not respond to home remedies. Three days later he was readmitted to the Homeopathic Hospital. His face was swollen, his legs were edematous, and his liver extended to the level of the umbilicus. His heart was no larger than it had been a month earlier, and the same systolic and diastolic murmurs were audible over the entire precordium. There was dullness over the middle lobe of the right lung, and both lungs were filled

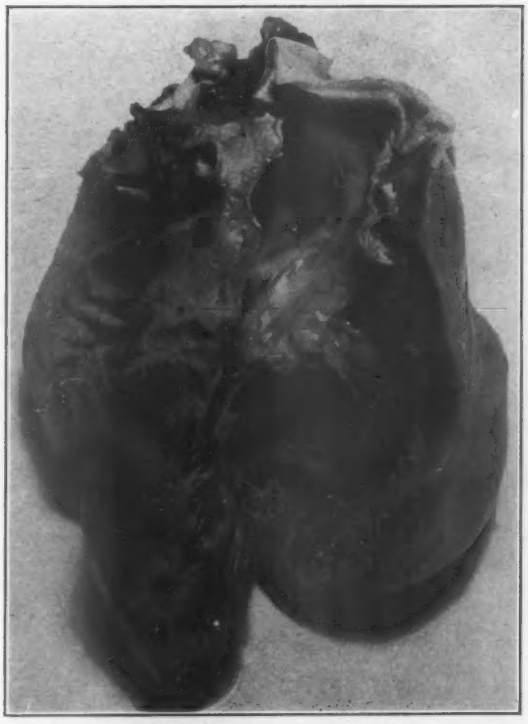

Fig. 1.—Photograph showing the relative thickness of the musculature of the right and left ventricles, indicating the pronounced hypertrophy of the left ventricle.

Fig. 2.—Photograph showing the mitral valve and interior of the left auricle. The corrugation of the auricular endocardium (MacCallum lesions), which is typical of rheumatic heart disease, is well illustrated. The shortening of the chordae tendineae and the knoblike thickenings along the valve margin are readily seen.

with moist, bubbling râles, but there was no evidence of free fluid in either pleural sac. He had passed no urine for twenty-four hours. The diagnoses were (1) rheumatic pancarditis with decompensation, and (2) bronchopneumonia. The intravenous injection of 50 c.c. of 25 per cent glucose and 1 c.c. of salyrgan, together with the oral administration of ammonium chloride, proved to be relatively ineffective. A transfusion of 60 c.c. of whole blood was given October 8, but the patient grew worse rapidly and died the next day. Three days before death the urine was essentially normal, the hemoglobin was 52 per cent, the erythrocyte count was 3,400,000 per cubic millimeter, the leucocyte count 15,000 per cubic millimeter; the differential leucocyte count showed 72 per cent polymorphonuclear cells and 28 per cent lymphocytes; the sedimentation rate was 30 mm. in an hour.

At autopsy* the veins of the neck and upper chest were congested, the abdomen enlarged, and the lower extremities slightly edematous. There was no pleural effusion. The entire middle lobe of the right lung, together with the adjacent portions of the upper and lower lobes, was airless and dark brown in color. The left lung was crepitant throughout, but exuded a frothy, bloody fluid. The pericardial sac contained more than the normal amount of fluid. The heart weighed 240 gm., an increase of about 400 per cent. The left ventricle was dilated and its wall was much thicker than normal. The heart muscle was deep red in color and tough in consistency. The free margin of the mitral valve was slightly thickened. The endocardium of the left auricle was somewhat corrugated, but elsewhere the endocardium was normal. The right auricle and ventricle were dilated. The aorta and pulmonary artery were normal.

Microscopic examination showed leucocytic infiltration about the small bronchi. The walls of the alveoli were thickened and fibrous, and the alveoli contained numerous desquamated cells of the type common in heart failure. Granulocytes were present in a few alveoli. Within the interstitial tissue of the myocardium there were inflammatory lesions consisting of round and plasma cells, with occasional giant cells, which were identified as Aschoff bodies. Many of these lesions were seen in relation to small coronary branches.

The final diagnoses were: (1) congestion of the kidneys, (2) congestion of the lungs and chronic interstitial pneumonitis, (3) bronchopneumonia, (4) chronic interstitial rheumatic myocarditis, (5) congestion and hyperplasia of the spleen, and (6) congestion and central necrosis of the liver.

COMMENT

The pathologic process in the lung was very similar to the so-called rheumatic pneumonia. The chronic nature of the pneumonitis and myocarditis warrants the assumption that the rheumatic infection was not of recent origin, and the accompanying photographs (Figs. 1 and 2) tend to substantiate this opinion. The probability is that the onset occurred between the ages of 18 and 24 months.

SUMMARY

A case of rheumatic heart disease in an infant, including necropsy observations, is reported. It is probable that first attacks of rheumatic fever frequently occur at a much earlier age than has been suspected.

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*Performed by Dr. Edward Fendrick.

ACUTE STAPHYLOCOCCIC VALVULITIS WITH VEGETATIONS OF RHEUMATIC TYPE*

Report of a Case

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FOR many years the etiology of rheumatic valvulitis has been a much debated question. Many believe that bacteria are responsible, but others consider the etiology unknown. Only a brief review of the literature is given because comprehensive reviews have recently been made by several writers (Jordan[1]).

Streptococcus viridans has been cultured from the blood stream of patients with rheumatic fever by Poynton and Payne,[2] Rosenow,[3] Swift and Kinsella,[4] Clawson,[5] Cecil, Nicholls, and Stainsby,[6] and others. The positive results have varied with the different investigators. Cecil obtained as high as 83.9 per cent positive results, using a modification of Clawson's technique. Improved technique apparently accounts for the greater number of positive cultures. Some variety of *Streptococcus viridans* is almost always encountered. The variety found most often by Clawson[5] was a type similar to *Streptococcus faecalis*. In seven cases in Cecil, Nicholls, and Stainsby's series[6] the joints were cultured. From five of these, *Streptococcus viridans* was obtained. Cecil believes that the streptococci enter the blood stream and produce septicemia, then localize in the joints in a manner similar to infectious arthritis, as for example, the gonorrheal variety.

Clawson, Bell, and Hartzell[7] have found that typical verrucae of acute rheumatic valvulitis are found in 75 per cent of cases of subacute bacterial endocarditis. They conclude that the larger bacterial vegetations are only a more severe degree of a similar process. This conclusion is based upon the fact that differentiation of borderline cases is difficult both pathologically and clinically. Von Glahn and Pappenheimer,[8] and Gross and Fried[9] agree that both lesions are found on the same valve frequently, but they believe them to be of separate etiology.

Gross and Ehrlich[10] regarded the Aschoff nodule as specific for rheumatic fever. Clawson,[11] on the other hand, found the Aschoff nodule in various conditions, such as puerperal sepsis, syphilis, and subacute bacterial endocarditis. He states that it is most commonly encountered in rheumatic fever but that it may occur in other infectious processes.

Colburn and Pauli[12] give evidence to show that throat infection with hemolytic streptococci is the first step in the rheumatic process. They

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find that the incidence of this throat infection checks with the geographic distribution of rheumatic fever. Studies on agglutinations, complement fixation, precipitin reactions, and antistreptolysins of sera from rheumatic patients also indicate that the hemolytic streptococcus is an important etiologic factor.

Inasmuch as bacteria are not demonstrable in the acute rheumatic verrucae, it has been suggested that rheumatic fever is caused by a virus. Schlessinger, Signy, Amies, and Bernard[13] have obtained what they believe to be elementary bodies from pleural and pericardial exudates of rheumatic patients. These are often agglutinated by the sera of rheumatic patients, especially when the disease is active and advanced. This does not occur in control sera from normals or patients with other diseases. They present two cases in which the serum agglutinated hemolytic streptococci but not the elementary bodies.

CASE REPORT

The case is that of a young man, 21 years old, who was first seen Dec. 11, 1937, complaining of marked pain in the great toe of his left foot. This had started two or three days before. Examination disclosed a bluish-black bullous formation covering the entire tip of the toe. This was surrounded by a narrow, red, inflamed area. The toe was sensitive to touch. He had a similar lesion on the tip of the middle finger of the right hand which had been present since Nov. 20, 1937; he had stuck this finger under the nail with a fork while washing dishes in a cafeteria a few days before. The infected area had drained three or four times and closed again. No drainage had occurred for three or four days, and during this time the toe had become sensitive.

He was sent home and advised to apply warm boric packs. Until this time he had felt well, having no complaints other than those referable to his toe and finger, and had continued his work.

Late the same afternoon, December 11, he became sick with headache, chills, sweats, and aching all over his body. He said he felt as if he were coming down with the grippe. That evening he had a temperature of 101° F. by mouth, a pulse rate of 110, generalized aching, nausea, and a moist warm skin. On December 12 the findings were the same except that he complained of more pain in his toe. His temperature was 101.4° F. and pulse rate, 110.

On December 13 he was very ill and was hospitalized. His temperature was 101.8° to 104.4° F. and pulse rate, 120 to 126. He became very restless and almost irrational at times. The skin was dry. The body, especially the extremities, was very sensitive to touch; he would cry out if an extremity was moved. There were two purplish-red papules about 5 mm. in diameter on the dorsum of the right forearm, and another in the right posterior lumbar region. He coughed often and had difficulty in clearing his throat. The sputum was often bloodstreaked. The pupils reacted to light. The throat was clear. There were no murmurs or thrills over the precordium. The lungs showed nothing abnormal. The liver was palpable 2 cm. below the costal margin and felt soft and tender. There was definite rigidity of the neck. Spinal puncture revealed a slightly turbid fluid under increased pressure. Thirty cubic centimeters of antimeningococcic serum were given intraspinally and 30 c.c. intravenously. About 11:00 P.M. a red papular rash appeared, covering both shoulders and the back.

The urine was amber colored, cloudy, and acid in reaction. Its specific gravity was 1.016. It contained a moderate amount of albumin (++), but no sugar. Micro-

scopic examination showed two hyaline casts, eight to ten granular casts, and two to five pus cells per low-power field. The leucocyte count was 10,800, of which 4 per cent were promyelocytes, 6 per cent myelocytes, 34 per cent stab forms, 52 per cent mature polymorphonuclear cells, and 4 per cent lymphocytes. A shift to the left was noted. No pneumococci of Types I, II, III, V, or VII could be found in the sputum. The sputum was bloody and contained numerous gram-positive cocci in pairs and chains. The spinal fluid contained a trace of globulin (Nonne-Apelt reaction) and sixty cells per cubic millimeter, but no organisms were found on smear. Roentgenologic examination of the chest revealed no positive changes.

On December 14 the patient was weaker and irrational. His body was very sensitive, and his neck was rigid. There were purplish-red nodules, 3 to 5 mm. in diameter, on the extremities and back. For the first time a soft to-and-fro murmur was heard over the fourth intercostal space, halfway between the sternal border and the nipple line. It radiated up to the third interspace, down to the fourth, and to the left of the nipple line. It could not be heard in the axilla. There was also a friction rub over the apex, best heard at the fifth rib, radiating down to the fifth intercostal space and to the left as far as the nipple line. The temperature was 103° F. in the afternoon, 102° F. at midnight. A blood culture, taken December 13, showed pure *Staphylococcus aureus;* there were over 200 colonies on the plate (a little more than 1 c.c. of blood was used). The blood Wassermann reaction was negative. Prontylin was given by mouth, and bacteriophage was given intramuscularly.

On December 15 his condition became very poor; his pulse was weak, and he was irrational and had urinary incontinence. He was given 300 c.c. of blood by vein. The systolic and diastolic murmurs were somewhat louder. The friction rub was coarser and extended up to the third rib. The temperature in the morning was 102° F., and in the afternoon 101° F.

On December 16 he was very irrational. The temperature rose to 105° F. at 4:00 P.M. with a respiratory rate of 38. Prontysil was given intraspinally and intravenously. The systolic and diastolic murmurs were more pronounced than on the preceding day. The friction sound became rough, loud, almost leathery, and was audible over the entire precordium. He was placed in an oxygen tent at 8:00 P.M. when it was discovered that he was becoming increasingly cyanotic. The temperature rose to 107° F., and he expired at 2:38 A.M., December 17.

The patient had always been in excellent health prior to the present illness except for the usual childhood diseases. He had bronchopneumonia at the age of 7 years, tonsillectomy at 7 years, chicken pox, measles, mumps, and whooping cough at the age of 10 years. He worked in a Civilian Conservation Corps camp during the summer of 1934 and was found normal on physical examination. He entered the University of Minnesota in September, 1934. The Health Service examination on entrance showed nothing abnormal.

On October 9, 1937, he was examined by Dr. Weisman for pain in the right lower abdomen. Nothing was found except an enlarged right inguinal ring. At that time he was working as a tinsmith and doing some very heavy lifting. No murmurs were present and the lungs were negative. The urine was normal and the leucocyte count was 7,750. He had never had any ailment similar to rheumatism, chorea, or growing pains. There was no history of chronic sore throat or of scarlet fever.

At autopsy the body was found to be well nourished and well developed, showing cyanosis, icteric sclerae, and petechiae over the neck, chest, arms, and legs. There was no edema. The left great toe was swollen and ecchymotic, with no ulceration. The right great toe had a similar appearance in a less degree. The tip of the middle finger of the right hand was swollen and ecchymotic, with no break in the epithelium.

The pericardial sac contained about 100 c.c. of seropurulent fluid. The serous surfaces were completely covered by a fibrinous exudate. The heart weighed 385 gm. and showed moderate dilatation of all four chambers with no gross hypertrophy. A continuous row of small white vegetations was found at the closure line of each mitral leaflet (Fig. 1). They were globular with smooth surfaces and were the typical verrucae of acute rheumatic valvulitis. However, some showed a fuzzy surface and were a little larger. This suggested the coexistence of bacterial lesions. There was no thickening of either leaflet other than that produced by the vegetations just mentioned. The other valves and the mural endocardium showed nothing of note. There was a small abscess in the interventricular septum and another in the left ventricular wall near the apex. The myocardium showed cloudy swelling.

Each lung was markedly congested and showed small areas of suppuration.

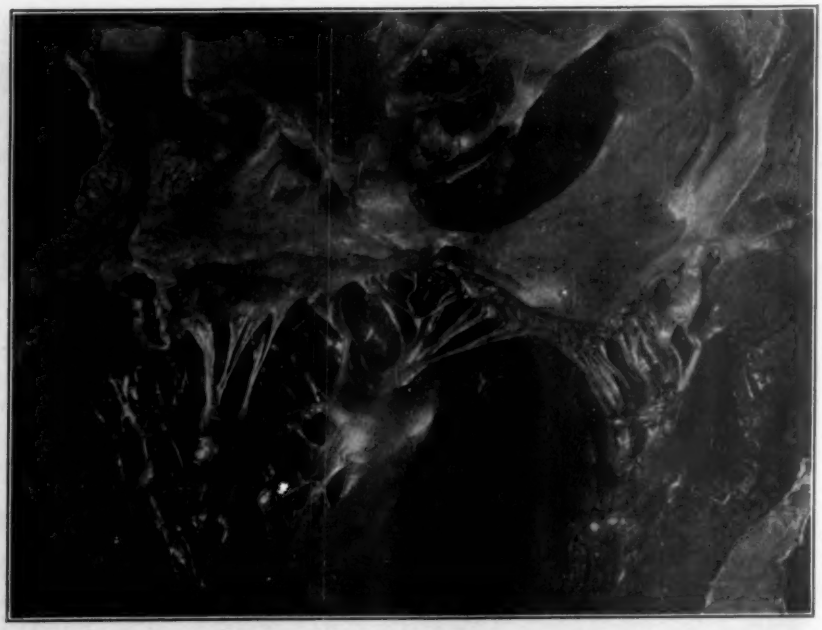

Fig. 1.—Row of vegetations on auricular surface of mitral leaflets. Photograph.

The spleen weighed 425 gm. An abscess 2.5 cm. in diameter was found; the remaining pulp was very soft.

Multiple small abscesses were found throughout the liver, which weighed 2,050 gm. Abscesses and septic infarcts were seen in each kidney, and there was also bilateral pyelitis. The mucosa of the pelves, ureters, and bladder was stained pink.

An abscess 4.5 cm. in diameter was found in the left frontal lobe of the brain with several small abscesses in the cerebral cortex bilaterally. There were small areas of suppuration on the superior surface of the brain. The spinal cord appeared normal.

A stained smear from the verrucae on the valve revealed staphylococci.

Microscopic study of the various organs revealed nothing of note except abscess formation together with clumps of gram-positive cocci. Acute inflammation of the meninges of the spinal cord was present. The majority of the vegetations on the

mitral valve were definitely rheumatic in type; there was a typical proliferative reaction with large oval nuclei and a somewhat basophilic cytoplasm; there was definite palisade arrangement of the cells. The surface endothelium was intact;

Fig. 2. Fig. 3.

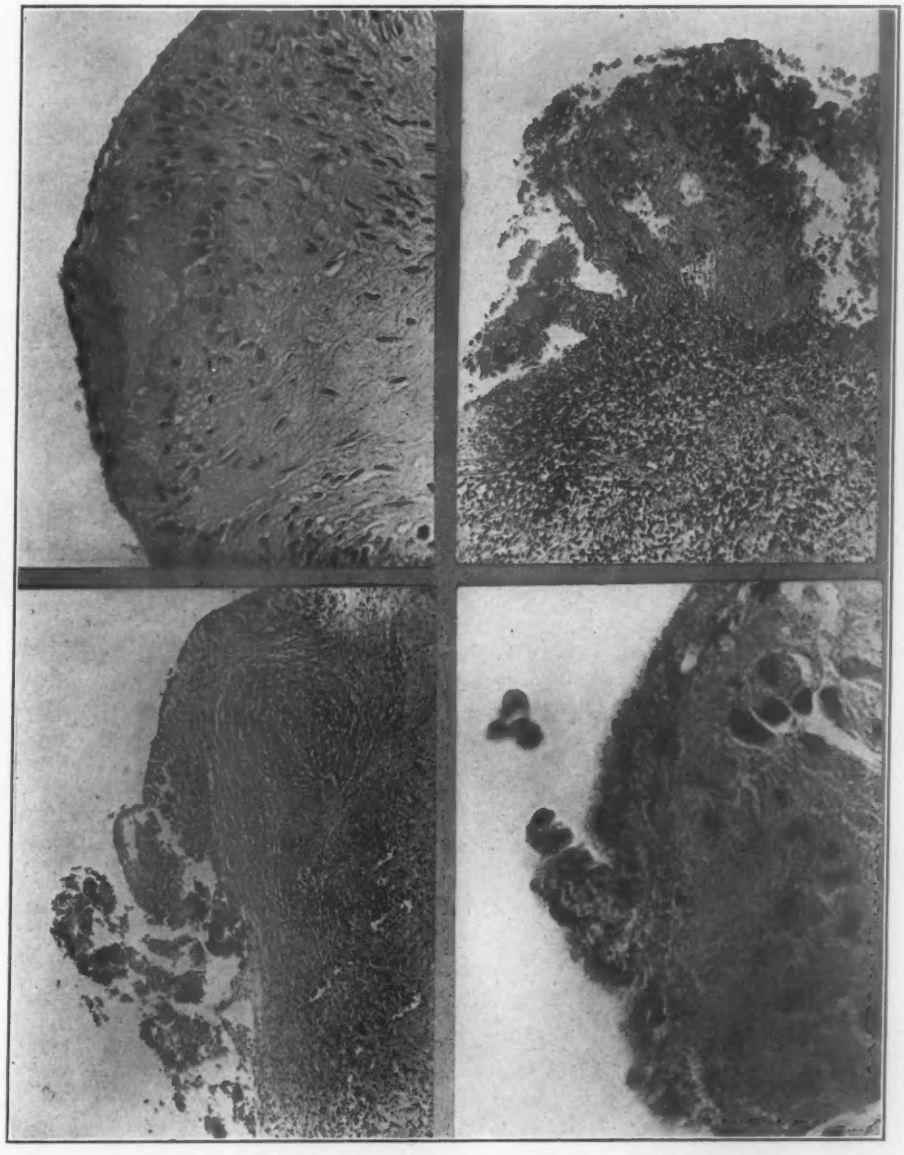

Fig. 4. Fig. 5.

Fig. 2.—Typical rheumatic vegetation. Note the hyaline necrosis under the intact endothelium. Photomicrograph.

Fig. 3.—Bacterial type of vegetation. Photomicrograph.

Fig. 4.—Transitional variety of vegetation; bacterial portion on left, rheumatic on right. Photomicrograph.

Fig. 5.—Transitional type of vegetation. Note rheumatic structure and bacteria near the surface. Gram stain. Photomicrograph.

under this there was a moderate amount of hyaline necrosis (Fig. 2). Some of the larger vegetations were composed of platelet material with numerous gram-positive cocci toward the surface and with a collection of polymorphonuclear cells at the base (Fig. 3). Other vegetations showed transitions between the rheumatic and the bacterial variety. Some were seen in which one part was typically rheumatic and an adjacent part was a bacterial lesion (Fig. 4). Others had a typical rheumatic structure except for the presence of bacteria near the surface. It may be that the last two varieties of vegetations were transitional forms (Fig. 5).

An acute polymorphonuclear exudative reaction was present in the mitral, tricuspid, pulmonary, and aortic rings. In the first three rings the inflammation was of a rather severe degree, more so than in the aortic ring. The pulmonary and tricuspid leaflets were acutely inflamed, the exudate being composed mostly of polymorphonuclear leucocytes. The cusps of the aortic valve were not involved.

A few small abscesses were present in the myocardium, many of which contained masses of staphylococci. There was a mild perivascular reaction composed mostly of polymorphonuclear cells. There were no Aschoff bodies.

Microscopic evidence of old rheumatic disease in the heart could not be found. The stigmata of old rheumatism described by Gross were not present. The pericardium showed acute fibrinous pericarditis and no evidence of past rheumatic disease.

DISCUSSION

In many cases of acute rheumatic endocarditis Clawson, Bell, and Hartzell[7] found vegetations on the valves that were identical microscopically with those of bacterial endocarditis. They insist that there are many transitions between rheumatic and bacterial vegetations on the same leaflet.

The history in this case indicates that a staphylococcic pyemia occurred, during the course of which signs of cardiac involvement appeared. There was no clinical evidence of a preceding acute rheumatic endocarditis. At autopsy the valve leaflets showed both typical rheumatic and typical bacterial vegetations with many transitional forms.

Two interpretations are possible: (1) A staphylococcic infection developed and produced lesions of both rheumatic and bacterial types as well as intermediate forms; (2) the patient had acute rheumatic endocarditis without clinical symptoms, and a staphylococcic infection was then superimposed which gave rise to bacterial vegetations. The numerous transitional vegetations seem to favor the first explanation.

SUMMARY

A case of staphylococcic pyemia is presented which showed many rheumatic, some small bacterial, and some transitional forms of vegetations on the mitral valve. It is suggested that vegetations of rheumatic type may be produced by staphylococci.

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Department of Reviews and Abstracts

Selected Abstracts

Katz, L. N., and Mendlowitz, M.: Heart Failure Analyzed in the Isolated Heart Circuit. Am. J. Physiol. **122**: 262, 1938.

A single isolated heart circuit is described for the study of the dynamics and energetics of spontaneous heart failure.

It is possible in this preparation to permit failure to occur with little or no change in total diastolic volume.

With the development of heart failure and with a relatively unchanged diastolic volume, there is a progressive decrease in the work and oxygen consumption of the heart and little change in its mechanical efficiency.

When the work of the heart is kept constant, no change in oxygen consumption or mechanical efficiency occurs, despite a progressive increase in the diastolic volume and the left auricular pressure.

These experiments demonstrate that heart failure must be defined in terms of a single chamber, rather than the heart as a whole.

It is concluded that failure of a heart chamber is due to an increase in load, a decrease in contractile power, or both, of such a degree that the chamber begins to fail to do the work imposed upon it by the load.

It is shown that loss of contractile power is manifested by a reduction in total energy release and hence work at a given diastolic volume and (except terminally) not by a decrease with which the liberated energy is utilized for mechanical work.

AUTHOR.

Karasek, F., and Poupa, O.: Seasonal Variations in the Sensitivity to Adrenalin of the Muscular Arteries of *Rana temporaria*. Compt. rend. Soc. de biol. **126**: 113, 1937.

The authors demonstrate by direct measure of the diameter of the lingual artery of the frog that it is more sensitive to adrenalin in the winter than in the spring and, more interesting still, find that in the female a marked loss of sensitivity occurs immediately after spawning.

STEELE.

Karasek, F., and Poupa, O.: Augmentation of the Vascular Effect of Adrenalin by Testosterone. Compt. rend. Soc. de biol. **126**: 116, 1937.

In the manner just described the tests show that three days after injection of 1 mg. of testosterone (perandren, Ciba) the lingual artery of the frog is more sensitive to adrenalin, and the authors state that in press is a similar piece of evidence presented by them, that folliculin also increases the sensitivity to adrenalin markedly.

STEELE.

Karasek, F., and Poupa, O.: Modification of the Vascular Effect of Adrenalin by Hormones of the Opposite Sex. Compt. rend. Soc. de biol. **126**: 118, 1937.

Using the same method the authors show that sex hormones of the opposite sex (testosterone in females, folliculin in males) gives rise to a decrease rather than an increase in sensitivity of the lingual artery of the frog to adrenalin.

STEELE.

Fleisch, A.: Concerning a Vasodilator in Erythrocytes. Arch. f. d. ges. Physiol. **239**: 345, 1937.

Hemolyzed red blood cell corpuscles obtained from the rabbit, dog, ox, and cat were found to have a marked effect upon increasing blood flow and lowering pressure in cats and rabbits. The author believes that a ferment present in the blood destroys the substance because in two hours the effect is more than half gone and because preserving the blood at 0° C., or with hydrocyanic acid 1/10,000 and heating prevents destruction of the substance. The substance is not soluble in ether, chloroform, or acetone, but is readily soluble in water. From biologic tests of its action upon various types of smooth muscle, he concludes that the substance is not acetylcholine, histamine, adenosin, or adenylic acid.

STEELE.

Fleisch, A., and Weger, P.: On the Appearance of Vasodilator Substances in the Blood. Arch. f. d. ges. Physiol. **239**: 354, 1937.

Using the two hind legs of a dog—one as "donor," in the circulation of which a Stromuhr and a cannula for removing samples of venous blood were placed, the other as "recipient," furnished with a pressure perfusion apparatus—venous samples of blood from one leg could readily be perfused through the other under various circumstances. Increase in flow through the perfused leg was taken as evidence of a vasodilator substance in the venous blood of the other leg. The authors found that under normal resting conditions almost no vasodilator substance was present in the venous blood but that after muscular work (electrical stimulation of the muscles of the donor leg) and with insufficient circulation large amounts could be shown to be present.

STEELE.

Fleisch, A., and Weger, P.: Vasodilatory Action of Phosphorrelated Metabolic Products. Arch. f. d. ges. Physiol. **239**: 362, 1937.

The hind legs of dogs were perfused in the manner described in the previous paper with blood to which was added numerous phosphoric acid compounds, and their effect compared with histamine and acetylcholine. Adenosin triphosphoric acid was found to be the most powerful vasodilator of all the phosphoric acids used, being active in 100 times greater dilution than the nearest competitor, muscle adenylic acid. The authors conclude, although the reasons are not quite clear, that the sum of the actions, all the intermediate products of metabolism, acetylcholine, adenosintriphosphoric acid, histamine, constitute an adequate stimulus for the vasodilatation which follows exercise.

STEELE.

Böger, A., and Wezler, K.: Calculation of Total Peripheral Arterial Resistance in Man. Arch. f. expér. Path. u. Pharmakol. **186**: 43, 1937.

The calculations are based upon the conception that arterial elasticity is as important as degree of contraction of arterioles in forming peripheral resistance.

He derives a formula which takes, he believes, better account of both these factors than a somewhat similar one of Broemser and Ranke's. The formula is $w = \left(\frac{Pd}{\triangle p} + \frac{h}{H}\right)\frac{E'\tau}{2}$ in which w is the functional resistance in dyne seconds per cm^5, $\left(\frac{Pd}{\triangle p} + \frac{h}{H}\right)$ an expression which serves to calculate mean pressure *(Pm)* by integration of the pulse curve based upon absolute pressures measured by a cuff and Korotokoff sounds, E' a coefficient of elasticity τ the duration of the pulse cycle. The present authors arrive at figures somewhat lower (roughly two-thirds) than Broemser and Ranke and show that the difference is chiefly due to the fact that the former workers calculated from the run off during diastole only, a period during which resistance is greater than during systole. Their normal average is given as 1842 dyne seconds per cm^5, about halfway between that of Frank and that of Broemser and Ranke. They point out that for some purposes the total average resistance, rather than that of a particular region, is an important conception.

STEELE.

Wezler, K., and Böger, A.: The Total Arterial Resistance Under Various Kinds of Sympathetic Stimulation. Arch. f. exper. Path. u. Pharmakol. **187**: 65, 1937.

In these studies the authors used their published method of calculating total peripheral resistance—a physical method dependent upon integration of pulse curves referred to absolute levels of pressure obtained by the usual auscultatory method and designed to account for elastic as well as frictional resistance. They investigated the effect upon this resistance of various sorts of sympathetic stimulation. With suffocation (holding the breath for 20-40 sec.) and on plunging the arm into a water-bath at 2° C. for 40 to 90 sec., rises of total resistance of from 50 to 100 per cent were regularly observed. Injection of sympathol was also followed by increased resistance, but adrenalin was, in contrast, followed by decreased total resistance. The most marked *decrease* (to one-fourth or to one-fifth the resting value) in total resistance was observed during recovery from strenuous muscular work. A method is appended for calculation of regional variations in resistance.

STEELE.

Spanner, R.: Circulatory Shunts in the Human Kidney; a Contribution to Knowledge of the Distribution of the Load Throughout Its Vascular System. Klin. Wchnschr. **162**: 1421, 1937.

There are three sites, according to Spanner, in the kidney where arterial blood can be shunted in considerable quantities directly to the venous side without traversing the glomerular and tubular vascular network. The first occurs in the small calices of the pelvis all over the wall where he could count as many as 18 arteriovenous anastomoses in 5 sq. mm., and in certain areas where there are "venous nests" as many as 23 in 2 sq. mm. The second site is in the cortex. He states that for years he has noticed that before 12 or 15 c.c. of a variety of materials is injected into the arteries, it can be found in the veins. Moreover, when he injects intra-arterially 30 per cent solution of kaolin-gelatin—a material which if not too warm, does not ordinarily pass through capillaries—it too can be found in veins. In cleared preparations it appears that the anastomosis here is between the lobular arteries and veins. The third place is in the capsule where the arteriovenous anastomoses occur in several ways, chiefly, capsular arteries to lobular veins and lobular arteries to capsular veins. The capsular vessels are derived from extrarenal sources. He promises a longer description soon.

STEELE.

Van Liere, Edward J., and Sleeth, Clark K.: Cardiac Hypertrophy During Pregnancy. Am. J. Physiol. **122**: 34, 1938.

The normal heart weight-body weight ratio in 90 normal adult female guinea pigs was found to be 3.17 grams per kilogram. Twenty-six animals were killed within seventy-two hours after they had given birth to their young; the HW/BW ratio in these animals was found to be 3.06. Twenty-seven pregnant animals were killed during the latter part of pregnancy and the HW/BW ratio was found to be 2.93. After the weight of the uterine contents had been subtracted from the body weight, however, the HW/BW ratio was found to be 3.17, that is, exactly the same as in the control animals. Corroborative data were also obtained from ten cats and seven dogs.

The conclusions drawn from this work are: 1. Pregnancy does not cause cardiac hypertrophy in the guinea pig. (Nor was there any evidence of cardiac hypertrophy in 10 pregnant cats and 7 pregnant dogs.) 2. Since pregnancy does not produce cardiac hypertrophy in three different types of animals, it seems doubtful that it would produce it in human beings. 3. Increased cardiac work does not necessarily produce cardiac hypertrophy.

AUTHOR.

Moritz, Alan R., and Atkins, Joseph P.: Cardiac Contusion: An Experimental and Pathologic Study. Arch. Path. **25**: 445, 1938.

The objective pathologic criteria for distinguishing between a cardiac contusion and a cardiac infarct vary in usefulness according to the age of the lesion. In the case of a recent myocardial lesion, the only evidence that should almost invariably serve to identify an otherwise indeterminate injury as an infarct is the finding of recent coronary occlusion. Pathologic changes more likely to be found in early contusion than in early infarction include massive interstitial hemorrhage, laceration, and tissue disorganization. Since all of these changes may be seen following spontaneous rupture of an early infarct, they are not conclusive. In the case of an older myocardial lesion there is no means of distinguishing objectively between contusion and infarction. Deposits of hemosiderin in myocardial scars are more likely to be seen in healed contusions than in healed infarcts, but, since hemosiderin is seen occasionally in healed infarcts, its presence is not conclusive. Three months after injury hemosiderin is found infrequently in traumatic scars, so that its absence in no way excludes the possibility of a lesion having been of traumatic origin. The presence or absence of remote coronary occlusion does not serve to identify a myocardial scar as having resulted from infarction or contusion, inasmuch as a heart which is the seat of occlusive coronary disease may have a superimposed traumatic lesion, and a heart with a large healed infarct may have no demonstrable coronary occlusion. The pathologic characteristics of the scars of myocardial contusion and infarction are frequently identical, and the presumptive nature of their origin must be determined by historical data rather than by post-mortem examination.

AUTHOR.

Holbrook, Arthur A.: Normal Venous Pressure as Determined by a Direct Method. Am. J. M. Sc. **195**: 751, 1938.

Normal venous pressure values obtained by various direct methods are quoted from the literature.

Venous pressures of 48 normal subjects determined according to the method of Griffith, Chamberlain, and Kitchel are presented in three tables. The first series was studied with the test arm "extended by the side in supination." In the second and

third series, the arm was abducted to at least a 70-degree angle and supported approximately as originally described by Moritz and Tabora. It was demonstrated that this single change in a technical detail accounted for greater accuracy in obtaining readings, more consistent results, and a lower range of venous pressure values.

Details of the technique used are given.

The normal range of venous pressure thereby obtained in 35 cases was from 10 to 100 mm. of physiologic saline solution, the average value being 65 mm. The older age group tended to have lower levels than the younger.

AUTHOR.

Fraser, Francis R.: The Clinical Aspects of the Transmission of the Effects of Nervous Impulses by Acetylcholine. Brit. M. J. 1: 1249, 1293, 1349, 1938.

(The Croonian Lectures delivered before the Royal College of Physicians of London.)

The acceptance of acetylcholine as the transmitter of the effects of nervous impulses throughout a large part of the peripheral nervous system has been followed by important advances in knowledge of the physiology of the autonomic nervous system and of voluntary muscle and neuromuscular stimulation. Already, in the few years since the principle gained general acceptance, a number of aspects of clinical value have emerged.

Many of the long-established therapeutic uses of atropine and physostigmine are explained.

Two new substances of therapeutic value have been introduced to clinical medicine—doryl and mecholine—and their value in the treatment of intestinal distention and atony, of postoperative and post-partum retention of urine, and of supraventricular paroxysmal tachycardia has been established.

A third new substance, prostigmin, has an established therapeutic value in the treatment of intestinal distention and atony and has so dramatic an effect on the muscle weakness and fatigue in myasthenia gravis that it has altered the outlook for patients suffering from this disease, and this therapeutic effect is of diagnostic value.

This action of prostigmin has led to an analysis of the cause of the muscular disability that seems likely to solve the problem of the cause of the disease.

Of greater importance, I believe, will be the discoveries that acetylcholine transmission will bring about in the future, for all processes, tissues, and organs of the body are affected by it. Further advances in pharmacology may be expected, for acetylcholine lends itself readily to modifications by the synthetic chemist. Emotional disturbances have been linked with skin lesions through acetylcholine, and observations have been recorded that must lead to a better knowledge of the functions of the central nervous system. And if acetylcholine transmission should be proved to occur there as well as in the periphery, still further advances in knowledge of clinical importance may be expected.

AUTHOR.

Benjamin, Julien E., Landt, Harry, and Culver, Laurence R.: The Body as a Volume Conductor and Its Influence on the Electrical Field of the Heart. Am. J. M. Sc. 195: 759, 1938.

Visual evidence is presented to confirm the accepted fact that the extremities act as volume conductors of the electrical potential generated in the heart.

The lungs transmit none of the differences in electrical potential registered in the electrocardiograms obtained by surface leads.

The lung pedicles act as the sole bridge for transmission of current to the lungs. These pedicles offer selective pathways of conduction.

The recent controversies as to the advisability of using the apex of the heart or the fourth interspace just to the left of the sternum for the site of preference of the right arm electrode in Leads IV and V, seem to accept, a priori, the dictum that the chest is a volume conductor. We are convinced that the descrepancies seen in these controversies can be explained on the basis that the chest is not a volume conductor.

AUTHORS.

Schlomka, G., and Witzenrath, W.: The Determination of the Relative Duration of Systole. III. Relative Systolic Duration in the Presence of Inverted T-Waves. Ztschr. f. Kreislaufforsch. 30: 281, 1938.

In 140 cardiac patients the duration of systole relative to the cycle length was measured. It was found that the presence of an inverted $T_{1 \text{ and } 2}$ (in 76 of them) did not shorten the relative duration of systole; in fact it tended to lengthen it.

KATZ.

Pines, Ign.: A Case of Functional Bundle Branch Block During Pregnancy. Wien. Arch. f. inn. Med. 32: 129, 1938.

The author describes a case of functional bundle branch block of the type known as that of Wolff, Parkinson, and White, which was observed during pregnancy. During this period one has to treat frequent attacks of paroxysmal tachycardia and paroxysmal fibrillation of the auricles. The attacks are interrupted by intravenous injection of ouabain and 20 seconds later pressure on the sinus caroticus. As a prophylactic the author has used with good result the composition of gynergen with quinidine and bromata. It is stated that functional bundle branch block does not lead to greater troubles during pregnancy than the simple paroxysmal tachycardia, provided that this block is not combined with any organic heart disease. As a consequence it is concluded that the functional bundle-branch block is not an indication for the interruption of pregnancy. The article contains also discussion of existing theories. The theory of Wolff, Parkinson, and White, the theory of H. Lohr, and the proposition of C. J. Rothberger are alike rejected with short justification. The theory of Holzmann and Scherf and Wolferth and Wood is also not accepted on anatomical, physiologic, and electrocardiographic grounds. The author believes that the cause of shortening of PR-distance in electrocardiogram is the shifting of pacemaker from sinus to the node of Aschoff-Tavara, as was thought by Wilson. The author is of the opinion that the functional bundle branch block is the result, not of the retardation of conduction of impulses through one of the bundle branches, but of acceleration in the other. On the basis of the appearance of many ventricular extrasystoles in his and other cases, he proves that one of the bundle branches has greater excitability than the other. As it is known that conduction of impulses is closely related to the excitability, one can admit that in functional bundle branch block one of the branches conducts more quickly than normal and more quickly than the other branch. At the end of the article the good result attained with gynergen in the prophylaxis of attacks is explained by the action of gynergen on the thyroid gland.

AUTHOR.

Block, C.: Heart Involvement and Electrocardiographic Findings in Anemia. Acta med. Scandinav. **93**: 543, 1937.

Individuals with anemia having marked cardiac symptoms, cardiac pain, and electrocardiographic changes in four leads (viz., low "voltage," depression of S-T segment and low or inverted T-waves) are not necessarily primarily cardiac patients since these symptoms and signs can be produced by the anemia and can disappear as the patient's anemia is improved. This study is based on the analysis of 88 anemic patients. The anemia is not always responsible for the cardiac symptoms and signs since they do not disappear as the anemia disappears.

KATZ.

Rytand, David A.: The Renal Factor in Arterial Hypertension With Coarctation of the Aorta. J. Clin. Investigation **17**: 391, 1938.

A consideration of hydrodynamics indicates that the arterial hypertension which is present in the upper part of the body in coarctation of the aorta may not be explained upon the purely mechanical grounds of obstruction to blood flow. In this condition there is an increased resistance in the smaller vessels (arterioles) which receive blood from the aorta proximal to the stenosis of its isthmus. The cause of this localized increased resistance is the same as the cause of the generalized increased resistance in a Goldblatt dog (with partially occluded renal artery); that is, interference with blood supply to the kidneys.

This conclusion is supported by the production of hypertension (cardiac hypertrophy) in rats by partial occlusion of the aorta proximal to one or both renal arteries. With partial occlusion of the aorta between the renal arteries, hypertension occurs only when living renal tissue is present distal to the occlusion; after simultaneous distal nephrectomy, hypertension never occurs even though there exists the same degree of mechanical obstruction to blood flow offered by the stenosis and presence of a collateral bed.

AUTHOR.

Gouley, Benjamin A.: The Evolution of the Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion. Am. J. M. Sc. **196**: 1, 1938.

The characteristic pneumonopathy of acute rheumatic fever can be identified as the precursor of an equally characteristic pulmonary change seen often in chronic rheumatic heart disease.

An intervening subacute stage is featured, as is the late chronic stage, by impaired elasticity of the lung tissue.

Histologic studies indicate that this pulmonary lesion is a chronic interstitial pneumonitis, which, like rheumatic myocarditis, is often accompanied by evidence of recurring inflammation.

One of its characteristic features is a hyperplasia of elastic tissue probably indicative of hypertensive strain in the fine pulmonary circulation.

This pulmonary change is not directly dependent on the presence of passive congestion or of mitral stenosis, since both of those factors may be absent or developed in variable degree. Passive congestion undoubtedly intensifies the interstitial fibrosis, but remains in our opinion a secondary factor.

AUTHOR.

Gouley, Benjamin A.: The Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evolution of Chronic Rheumatic Heart Disease. Am. J. M. Sc. **196**: 11, 1938.

The author discusses the probability that: (1) mitral stenosis in some patients is in itself not the sole or possibly even an important factor in the causation of the chronic right heart failure which characteristically terminates chronic rheumatic heart disease; (2) such failure may occur even in the absence of significant mitral valvular dysfunction; (3) the key lesion in this particular type of patient is the association of an intrapulmonary lesion with right ventricular strain; (4) the intrapulmonary lesion is a diffuse fibrosis that at least in its beginning is a direct result of rheumatic pneumonitis; (5) the factor of passive pulmonary congestion becomes important with the development of left ventricular failure which may or may not occur.

AUTHOR.

Wallgren, Arvid: Rheumatic Erythema Nodosum. Am. J. Dis. Child. **55**: 897, 1938.

Rheumatic erythema nodosum should be sought among those who react negatively to tuberculin. To prove erythema nodosum is due to rheumatic fever when a tuberculous infection is present at the same time is hardly possible, considering the connection that has been shown to exist between tuberculosis and erythema nodosum. But that does not signify that an erythematous eruption in a tuberculous child must have been produced by tuberculosis.

One may consider rheumatic fever as the cause of erythema nodosum only on condition that the child is not infected with tuberculosis. It is essential that a child be examined for tuberculosis when he has acute rheumatism during which erythema nodosum appears.

MCCULLOCH.

Seely, Hall: Primary Obliterative Pulmonary Arteriolar Sclerosis. J. A. M. A. **110**: 792, 1938.

This case is the only one of its kind in a series of more than 3,800 autopsies at the New Haven Hospital. Its infrequence is attested by McCallum in a report of a similar case, the only one in a series of 12,000 autopsies at Johns Hopkins Hospital. If Ayerza's disease is primarily a syphilitic pulmonary arteritis or a syphilitic bronchitis (the two concepts of Ayerza's two most interested pupils), the present case is not one of Ayerza's disease. The Wassermann reaction was negative. The lumina of the pulmonary arterioles were greatly reduced by fibrotic changes, with no evidence of inflammatory reaction. Arteriolar changes such as described in the lung were found in no other tissue. The bronchial mucosa was smooth and shining, and free from exudate or obstructive lesions. Marked eccentric hypertrophy and dilatation were found limited entirely to the right ventricle. The aortic and pulmonary cusps appeared intact and competent. Symptoms of cardiac decompensation were of one month's duration. The patient was not clearly polycythemic but was markedly cyanotic. On admission to the hospital she did not appear acutely ill but died rather suddenly on the third day. No evidence of disease of the coronary arteries or of the myocardium was found at post-mortem examination.

MONTGOMERY.

Lewis, W. H., Jr.: Changes With Age in the Blood Pressure in Adult Men. Am. J. Physiol. **122:** 491, 1938.

There has been no satisfactory statistical analysis of the blood pressures in later life, particularly after the age of 60 years. This study has been carried out in order to obtain further information as to the change in blood pressure incident to increasing age. One hundred healthy men, aged from 40 to 89 years, have been studied. Measurements of the blood pressure were made with a mercury manometer by the auscultatory method. Blood pressures were taken in the basal state in the morning after fasting for fourteen hours. The data have been statistically analyzed, and the results indicate that the systolic blood pressure rises continuously after the age of 40 but the greatest rise occurs after the age of 65. Between the ages of 40 and 65 there is an average increase of only 8 mm. in the twenty-five-year span, whereas between the ages of 65 to 90 there is an average increase of 34 mm. The mode of the systolic blood pressure, of the mean, and of the pulse pressures increases with age. The average diastolic blood pressure varies slightly in succeeding decades, but there is no significant increase with age as in the systolic blood pressure. This is in accord with the general view that the diastolic blood pressure level is unaffected by age.

HINES.

Glenn, F., Child, C. G., and Page, I.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs. Am. J. Physiol. **122:** 506, 1938.

In order to determine, if possible, the relationship between the central nervous system and experimental hypertension, hypertension was produced by the Goldblatt method in five dogs, and the cord was destroyed below the level of the fifth cervical vertebra. Daily blood pressure observations were made over a control period of two weeks, using a van Leersum carotid loop, and hypertension was produced by the application of Goldblatt clamps to the renal arteries. Following this, daily blood pressure observations were made for one month or more, and, if the blood pressure remained elevated, a laminectomy was performed and the spinal cord was sectioned in the low cervical region. Daily blood pressure readings were again obtained until the animal was killed. In all the dogs the destruction of the spinal cord was followed immediately by a sharp fall in blood pressure to below previous normal levels. The blood pressure subsequently returned to a level above the previous normal readings for the animal but did not return to the previous maximal hypertension levels and tended to fall towards the end of the period of observation.

HINES.

Seiro, V.: Concerning Blood Pressure and Circulation in Varicose Veins of the Lower Extremities. Acta chir. Scandinav. **80:** 41, 1937.

The author has investigated pressure in the cutaneous veins in the lower limbs. Individuals with varicose veins as well as normal persons were studied. He found that the level of the fluid in the manometer rose usually to the level of the heart, occasionally somewhat lower. The pressures were approximately similar in persons with and without varices. The absolute pressure in the manometer depends on the site of the puncture and the height of the subject. The main factor in production of venous pressure in a person standing at ease is undoubtedly hydrostatic pressure, but certain physiologic activities, respiration and muscular activity of the limbs, cause it to vary. Deep inspiration or activity of

the muscles in the limbs lowers the pressure; deep expiration raises it. If the valves are intact, the fall is considerable, if incompetent the fall is less noticeable. But if, in the latter case, the vena saphena magna is compressed above the site of puncture, and the subject makes continuous walking movements, the pressure falls nearly to the same degree as for intact valves. This supplies us with a surer method of ascertaining the competency of the valves. Simultaneous measurement of pressure in the deep and superficial veins lead the author to conclude that the blood in the venous circulation of the lower limbs flows from the cutaneous veins through the anastomosing vessels into the deep veins and leaves the limbs through the latter. This is certain during muscular activity and is probably true for the erect posture.

STEELE.

Slany, A.: The Relation of Anomalies of the Circle of Willis to the Formation of Aneurysms in Vessels at the Base of the Brain. Virchows Arch. f. path. Anat. **301**: 62, 1938.

The author records 26 cases of aneurysm of the arteries at the base of the brain encountered during the past decade. Fourteen of these exhibited congenital defects of the circle of Willis, but, in four of these fourteen, recurrent endocarditis was also found and had, therefore, to be considered as a possible cause of the aneurysm. It is interesting to note that four patients suffered, presumably, from arterial hypertension. He concludes naturally that anomalies of the circle of Willis are important in the development of aneurysm in the neighborhood.

STEELE.

De Takáts, Geza: Vascular Accidents of the Extremities. J. A. M. A. **110**: 1075, 1938.

The author summarizes, at some length, the clinical picture, abnormal physiology, and treatment of arterial hemorrhage, arterial embolism, arterial thrombosis, venous hemorrhage, and venous thrombosis. Though surgical measures are frequently essential to proper treatment, of no less value is painstaking care by a physician who is capable of accurately diagnosing, localizing, and treating the special vascular emergency.

Though it is impossible in a summary to include most of the sharply drawn decisions for treatment of one or another such emergency, several of the more important, less well known ones will be mentioned: (1) Ambulatory treatment of thrombophlebitis is preferred to that of prolonged bed rest with one important exception—thrombosis of the perforating veins of the muscles of the calf of the leg. There is a high incidence of pulmonary embolism if prolonged bed rest is not enforced and venous ligation is not performed. (2) Sudden vascular occlusion, by any process, usually is quickly followed by spasm in nearby vessels. This spasm, untreated, is frequently the cause of loss of limb, and yet the spastic vessels are successfully subject to treatment by various vasodilating procedures such as mild heat, intravenous papaverine, or intravenous sodium nitrite. (3) Limbs endangered by arterial embolism have frequently been saved by such procedures, but if signs of inadequate circulation persist for more than an hour or two, embolectomy should usually be performed. Statistics show clearly its value in selected cases. Since the upper extremities are much less subject to gangrene by major arterial occlusion than are the lower extremities, embolectomy in the upper extremities is rarely performed.

MONTGOMERY.

Blasingame, F. J. L.: Thrombotic Occlusion of Superior Vena Cava and Its Tributaries, Associated With Established Collateral Circulation. Arch. Path. 25: 361, 1938.

No history was available. The pathologic finding was that of chronic, complete thrombosis of the superior vena cava, with complete occlusion of both innominate veins. There were some thrombi in the internal jugular and axillary veins, but not sufficient to prevent collateral circulation via the external jugular, transverse cervical, transverse scapular, and azygos veins, to the inferior vena cava. The veins of the upper extremities were larger than usual. A detailed description of the collateral pathways is given.

MONTGOMERY.

Springorum, P. W.: The Importance of the Cutaneous Vessels for the Systemic Circulation. Klin. Wchnschr. 17: 11, 1938.

Simultaneous records of arterial pressure (intra-arterial cannula) and blood flow to and from a given area of skin (one Rein's Stromuhr on the artery to, and a second on the vein from, the area) show that the skin is a not inconsiderable depot for blood. The animals studied were dogs. When histamine is injected, blood is detained in the skin, and, when veritol or adrenalin is injected, blood is released.

A second experiment illustrates the importance of the skin as a blood depot under the influence of heat. If the arterial pressure, cutaneous and muscular blood flows are measured simultaneously, it becomes clear that, when the skin is exposed to a heat lamp, the blood flow through the skin may increase threefold to sixfold and at the expense of flow through the muscles. If the animal has first been bled, so that he is more sensitive to loss of blood into the skin, warming the skin can induce sufficient fall in arterial pressure to cause collapse. He suggests that caution is, therefore, necessary in application of heat to the skin of individuals who are, for any reason on the verge of collapse.

STEELE.

Altscshule, Mark D., and Gilligan, D. Rourke: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: II. The Dynamics of the Circulation. J. Clin. Investigation 17: 401, 1938.

The effects of the intravenous injection of isotonic and of slightly hypertonic crystalloid solutions on the venous pressure, pulse rate, arterial pressure, cardiac output, velocity of blood flow, respiratory dynamics, electrocardiogram, and blood volume of normal man have been studied.

When 500 to 1500 c.c. of physiologic saline, 5 per cent glucose, or 5 per cent glucose in physiologic saline solutions, were injected at rates of less than 20 c.c. per minute, very slight changes were observed in the cardiovascular functions studied; the blood volume was usually considerably increased.

When these volumes of fluid were injected at more rapid rates considerable increases in venous pressure, cardiac output, velocity of blood flow, and in blood volume were usually observed; increases in pulse rate, pulse pressure, and in the P-wave of the electrocardiogram were observed in some instances.

The greater venous pressure increases occurred in subjects who received fluids in the larger volumes and at the more rapid rates. The venous pressure invariably returned to the control level within ten to twenty-five minutes after the end of fluid administration.

Significant increases in cardiac output occurred in patients in whom the intravenous injection of fluids resulted in rises in venous pressure.

When fluids were injected in larger volume and at more rapid rates, the increase in velocity of blood flow was considerably less than that expected from changes in the cardiac output. In some instances the increase in velocity of blood flow was greater after the injection of 500 c.c. of fluid than after 1000 or 1500 c.c. These findings are interpreted as indicating an increase in pulmonary blood volume during injection. Dyspnea did not occur, and changes in respiratory dynamics were not observed.

The fact that rises in venous pressure did not persist, or even did not occur, in spite of increased blood volume, together with the observation of increasing diffuse flush of the skin, points to a progressive peripheral vasodilatation during the course of injection of fluids. Additional evidence in this regard is the tendency toward increased pulse pressure observed in some subjects.

The clinical implications of these findings are discussed.

AUTHOR.

Veal, James Ross: Factors in the Mortality Rate of Arteriosclerotic Gangrene: A Comparative Study of 214 Cases of Surgical Intervention. J. A. M. A. 110: 785, 1938.

Diabetic gangrene is not included. A series of 110 cases of amputation for arteriosclerotic gangrene performed in the New Orleans Charity Hospital in the five-year period ending in 1933 resulted in a mortality of 39.1 per cent. During the next three-and-one-half-year period, a series of 104 such cases had a mortality of 28.8 per cent. An explanation for the lowered mortality seems to rest in more careful preoperative and postoperative care: prompt amputation, free use of fluids, infusions of dextrose, frequent moving of the patient, early postoperative removal from bed to chair, keeping the amputation stump in a dependent rather than an elevated position, and the use of a heat cradle at not more than 100° F. In both series the commonest cause of death was pneumonia, the incidence of which was lowered a little in the recent series. Shock was the second commonest cause of death in the first series but the sixth cause in the recent series. Cardiac failure (congestive failure and coronary thrombosis) was the fourth cause in the first series but the second cause in the recent series. The incidence of cardiac failure in the recent series was nearly double that in the first series.

Three factors pointing to poor prognosis are extensive gangrene, evidences of arteriosclerosis in vital organs, and preoperative fever. Gas gangrene was an infrequent complication. Primary healing occurred in only 35 of the 54 patients surviving amputation. Recurrent gangrene carried a very high mortality. Some roentgenologic evidence is presented with the theory that emboli from the amputation stump are a cause of postamputation pneumonia. It is suggested that infusions of dextrose rather than of saline solution may help prevent cardiac failure associated with acute pulmonary edema.

MONTGOMERY.

Kandel, E. V.: Fever of Undetermined Origin in a Patient With Traumatic Brachial Aneurysm Cured by Excision. J. A. M. A. 110: 891, 1938.

The patient had pain for four years in the site of what proved to be the aneurysm. He had chills, fever, nausea, and vomiting for the month and a half immediately preceding excision of the aneurysm. Symptoms ceased when the aneurysm was excised. Culture of its tissue yielded a diphtheroid bacillus. Microscopic examination of the tissue showed only remnants of chronic inflammation. No blood cultures were reported.

MONTGOMERY.

Bazett, H. C.: Some Principles Involved in Treatment by Heat and Cold. Med. Record **147**: 301, 1938.

Various workers have given statistics for the seasonal distribution of initial attacks of symptoms of angina pectoris, coronary occlusion, myocarditis, endocarditis, thrombosis, embolism, cerebral hemorrhage and aneurysm. Data of this kind collected by Dr. L. B. La Place, for the author, show that the incidence is greatest at the times that the physiologic strain would be expected to be greatest—namely, at the times of sudden climatic changes, early summer, and particularly at the onset of cold in the autumn. The highest peaks are in November and February; the minimum, in August. Vasoconstriction imposed by a sudden increase in cold obviously puts an immense strain on the circulatory system. Possibly this strain is partly dependent on the presence of the large blood volume of summer. Patients of such a type should be carefully guarded from sudden exposure to cold after acclimatization to heat treatment. If the theory is sound, then at the completion of a series of heat treatments during which the patient has also been kept under warm conditions, bleeding before returning him to a cold climate might be sound prophylaxis in selected cases.

MONTGOMERY.

Brown, James Barrett: The Interstitial Radiation Treatment of Hemangiomata. Am. J. Surg. **39**: 452, 1938.

All hemangiomas that exhibit any growth tendency should be treated early. Arterial hemangiomas may present trying therapeutic problems when both their presence and their treatment threaten the patient with deformity. Cautery destruction or surgical excision should be used in areas where the scar does not show. Radiation, properly given, does not scar. Because most hemangiomas have elements some distance from the surface, interstitial rather than surface radiation is advisable. The interstitial implantation of gold radon seeds in the author's experience is the most valuable single method of therapy where surgical excision or surface radium is not applicable. Usually within a week's time there is a definite decrease in the blood flow through the tumor. The reaction reaches its peak within two to three weeks, and shortly after this the most speedy recession of the growth is noted. Progressive improvement may follow for six months following a single treatment. Even large involvements may be stopped with a single treatment, where it has been recognized that months or even years might be necessary with surface radiation.

MONTGOMERY.

Krock, Fred H.: A Simplified Apparatus for Pressure-Suction Therapy of Obliterative Arterial Disease of the Extremities. South. M. J. **31**: 294, 1938.

The remarkable development of collateral circulation occurring in some cases of organic obliterative arterial disease of the extremities following the use of pressure-suction therapy is so striking that this form of treatment has become almost standard in the past four years. The apparatus has, however, been expensive; ranging in price from $350 to $1000. A simplified apparatus, which has long life and an even wider range of pressures, has been designed. The entire equipment with two boots and two complete sets of cuffs can be constructed for slightly less than $100. No manufacturer is named.

MONTGOMERY.